Department of Chemistry
and Chemical Biology,
Harvard University

Challenging Problems in
Chemistry and Chemical Biology

# Selections from the Evans Database of Elementary and Advanced Problems in Organic Chemistry

*(Including problem set and exam questions from Chemistry 30 and 206 at Harvard University)*

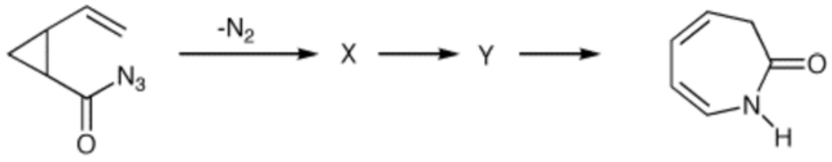
## Elementary Organic Chemistry

### Problem 440

Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz

Upon thermolysis, **1** undergoes loss of $N_2$ to give intermediate X which undergoes thermal reorganization to Y and final tautomerization to **2** (Vögtle, *Liebigs Ann. Chem.* **1965**, *682*, 1). Identify intermediates X & Y and provide a mechanism for the transformation of **1** to **2**.

**1**



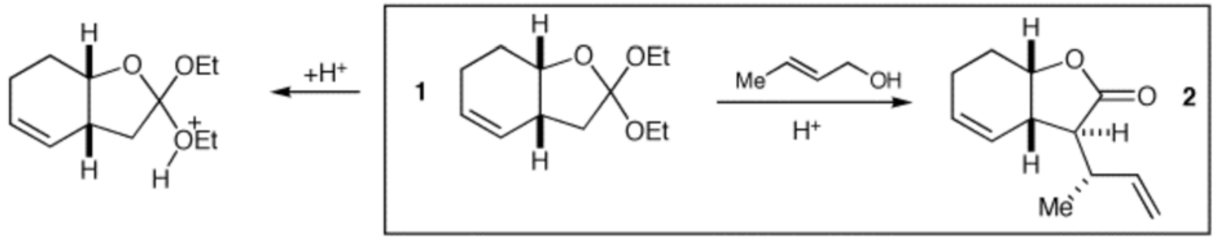
**2**

Provide your answer here.

### Problem 441

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1987**, *52*, 3541
Keywords: Mechanism quiz

When treated with 2-butene-1-ol in the presence of an acid catalyst, **1** is stereoselectively transformed into lactone **2**. ( Kozlowski, *J. Org. Chem.* **1987**, *52*, 3541). Provide a mechanism for this transformation below. In your mechanism you are not required to deal with the issue of stereochemistry.



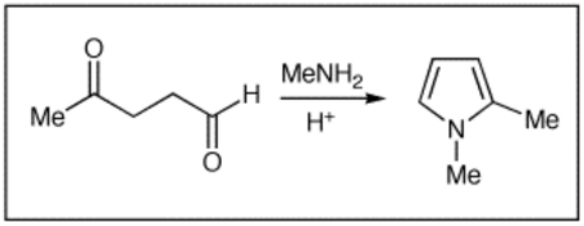
### Problem 451

Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz

In transformation shown below there are one or more intermediates intervening between reactant(s) and product(s). Propose a mechanism to account for the observed transformation.

*Note: In your answer, draw intermediates but not transition states.*

**Your Mechanism:**

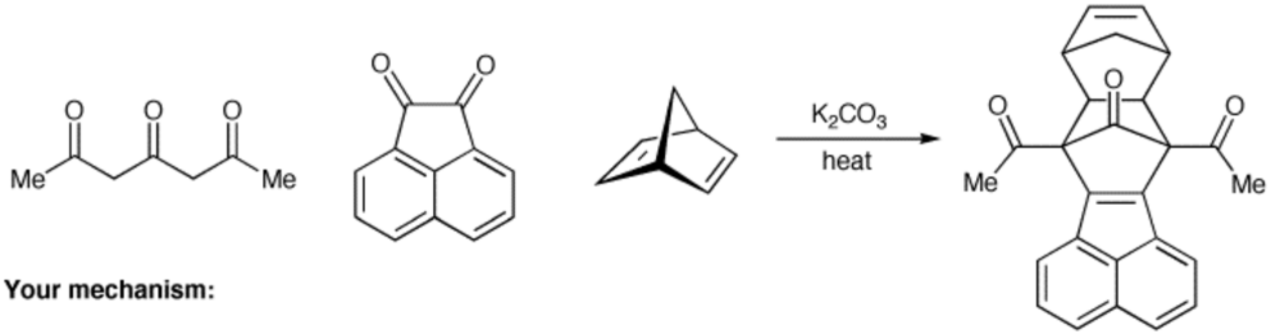


## Problem 455

Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz

The transformation shown below was presented in a recent Harvard seminar by Professor L. T. Scott from Boston College. Propose a mechanism to account for the observed transformation.

Please answer the question in the space provided below. *Note: In your answer, draw intermediates but not transition states.*

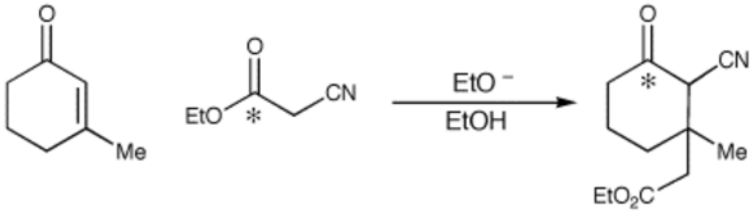


**Your mechanism:**

## Problem 456

Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz

The following reactions is an example of what is referred to as the "abnormal Michael Reaction." Provide a mechanism for this reaction that is consistent with the isotope labeling pattern shown ([ = $^{14}C$). Please answer the question in the space provided below. If you cannot solve the complete mechanism, proceed as far as you think the reaction logically proceeds. Partial credit will be given.



**Your mechanism:**

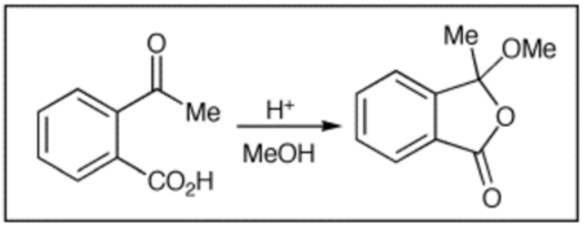
## Problem 461

Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz

In the transformation shown below there are one or more intermediates intervening between reactant(s) and product(s). Propose a mechanism to account for the observed transformation.

*Note: In your answer, draw intermediates but not transition states.*

**Your Mechanism:**



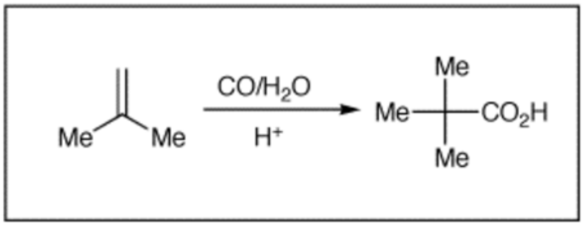
## Problem 462

Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz

In the transformation shown below there are one or more intermediates intervening between reactant(s) and product(s). Propose a mechanism to account for the observed transformation.

*Note: In your answer, draw intermediates but not transition states.*

**Your Mechanism:**

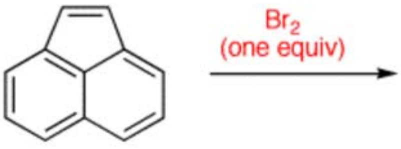


## Problem 465

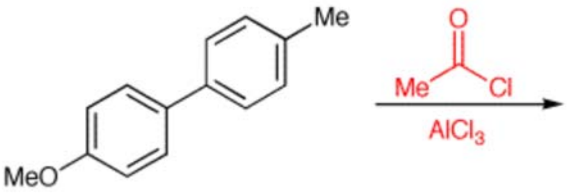
Contributer: **David A. Evans**
Citation:
Keywords: Reaction quiz

Predict the **major** product of the illustrated reactions. Place your answer in the spaceprovided. Draw that product which is isolated after neutralization and a conventional extraction.

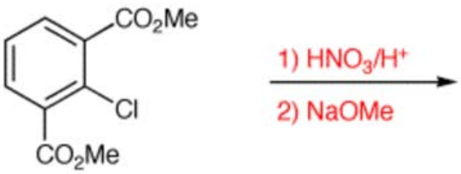
**Part A (5)**



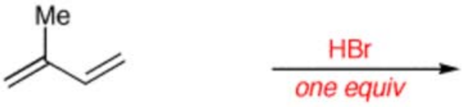
**Part B (5)**



**Part C (5)**

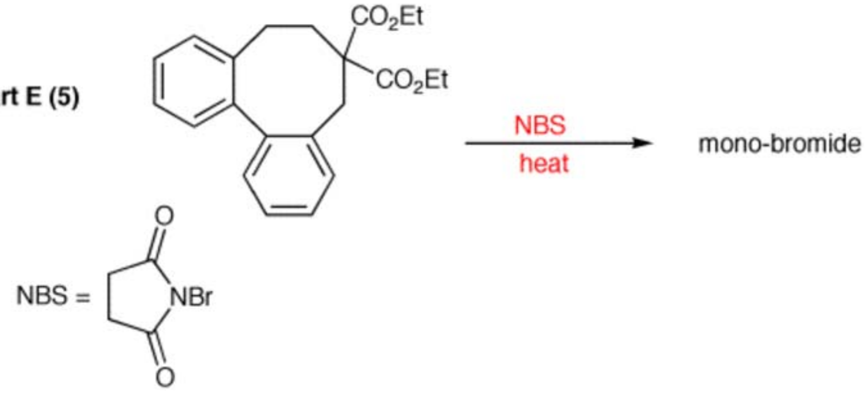


**Part D (5)**



*hint: assume electronic effects are dominant*

**Part E (5)**



## Problem 466

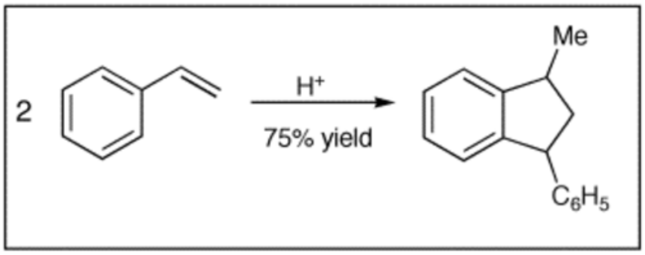
Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz

In each of the transformations shown below there are one or more intermediates intervening between reactant(s) and product(s). In each instance, propose a mechanism to account for the observed transformation.

*Note: In your answer, draw intermediates but not transition states.*

**The Transformation:**

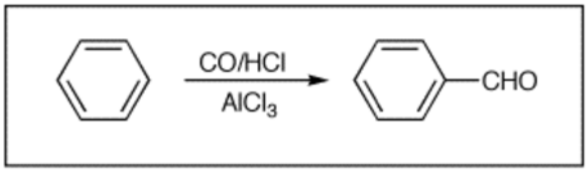
**Your Mechanism:**



**The Transformation:**

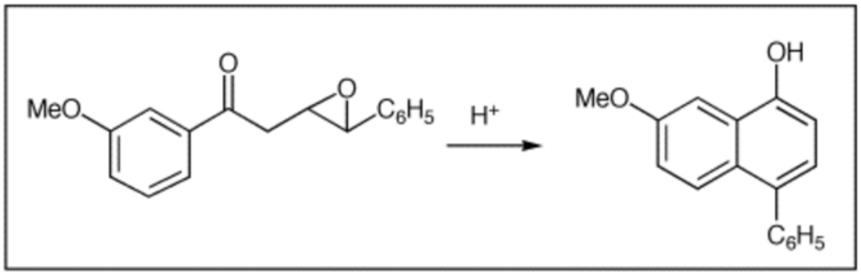
This reaction is called the Gatterman-Koch aldehyde synthesis.Hint: You will probably solve the mechanism when you determine the compound formed in the CO + HCl reaction.

**Your Mechanism:**



**The Transformation:**

**Your Mechanism:**



## Problem 471

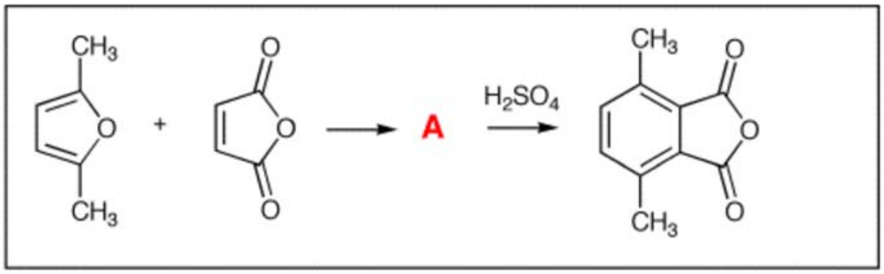
Contributer: **M. Loudon**
Citation:
Keywords: Mechanism quiz

The Diels-Alder reaction between 2,5 dimethylfuran and maleic anhydride gives compound **A**. A subsequent acid-catalyzed transformation affords 3,6-dimethylphthalic anhydride. Deduce the structure of compound **A** and provide a mechanism for the conversion of **A** into 3,6-dimethylphthalic anhydride. (*Organic Chemistry, 4th Edition*, G.M. Loudon, pg. 741)

*Note: In your answer, draw intermediates but not transition states.*

**The Transformation:**

**Your Mechanism:**

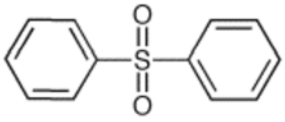


## Problem 472

Contributer: **M. Loudon**
Citation:
Keywords: Mechanism quiz

Diphenylsulfone (shown below) is a by-product that is formed in the sulfonation of benzene. Provide mechanisms for the formation of both benzenesulfonic acid and diphenylsulfone. (*Organic Chemistry, 4th Edition*, G.M. Loudon, pg. 741)

*Note: In your answer, draw intermediates but not transition states.*



**Diphenylsulfone**

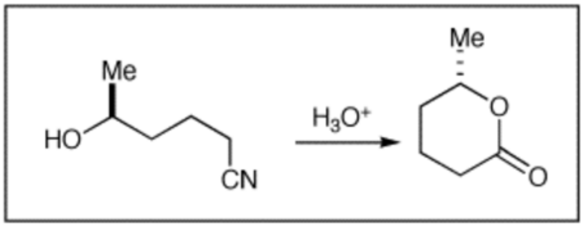
**Your Mechanism:**

## Problem 473

Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz

In the transformation shown below there are one or more intermediates intervening between reactant(s) and product(s). Propose a mechanism to account for the observed transformation.

*Note: In your answer, draw intermediates but not transition states.*



**Your Mechanism:**

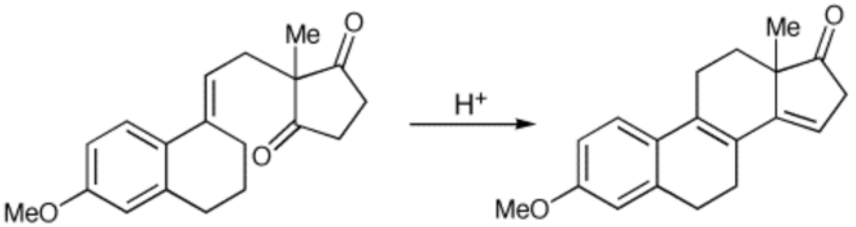
## Problem 477

Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz

Provide a plausible mechanism for the illustrated acid-promoted transformation.

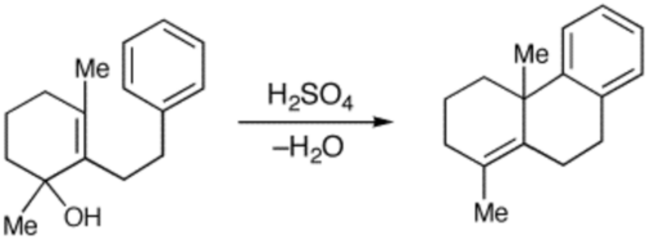
*Note: In your answer, draw intermediates but not transition states.*

**Part A:**



**Your Mechanism:**

**Part B:**

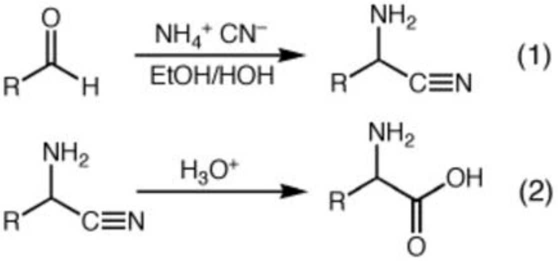


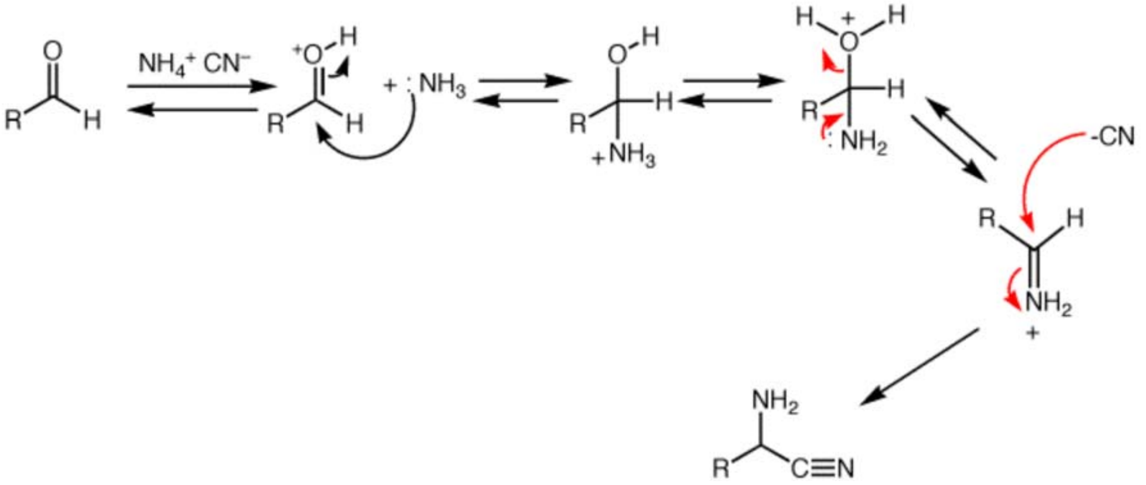
**Your Mechanism:**

## Problem 481

Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz

One of the best methods of synthesizing racemic alpha amino acids is through the *Strecker Amino Acid Synthesis* which consists of the two-stage operation shown on the right.
In the space below provide a detailed mechanism for the reaction identified as equation (1). Intermediates but not transition states should be illustrated.

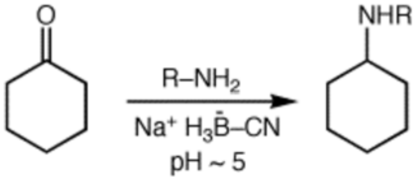




## Problem 482

| | |
|---|---|
| Contributer: | **David A. Evans** |
| Citation: | |
| Keywords: | Mechanism quiz |

Ketones and aldehydes may be *reductively aminated* with the reagent sodium cyanoborohydride at pH ~ 5. The only special attribute of this borohydride reagent is that it is stable in weakly acidic media. In the space below provide a detailed mechanism for the illustrated reaction. Intermediates but not transition states should be illustrated.

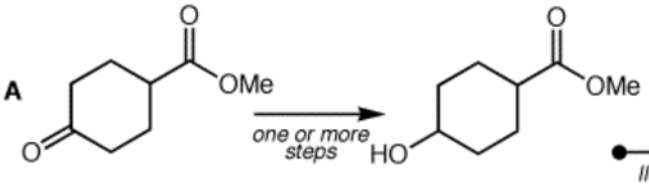


## Problem 485

| | |
|---|---|
| Contributer: | **David A. Evans** |
| Citation: | |
| Keywords: | Reaction quiz |

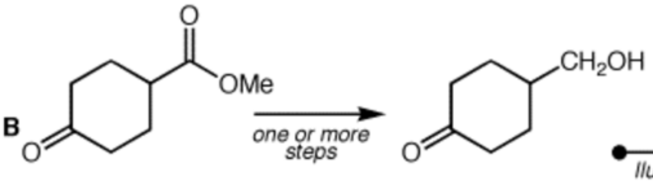
A series of transformations is provided below. Provide either the optimal reagent or illustrate the most efficient set of reactions to accomplish the indicated transformation. Your grade will depend on both efficiency and feasibility.

**Part A**



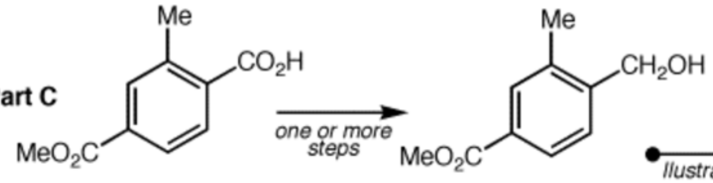
*Illustrate optimal reagent or sequence for this transformation*

**Part B**



*Illustrate optimal reagent or sequence for this transformation*

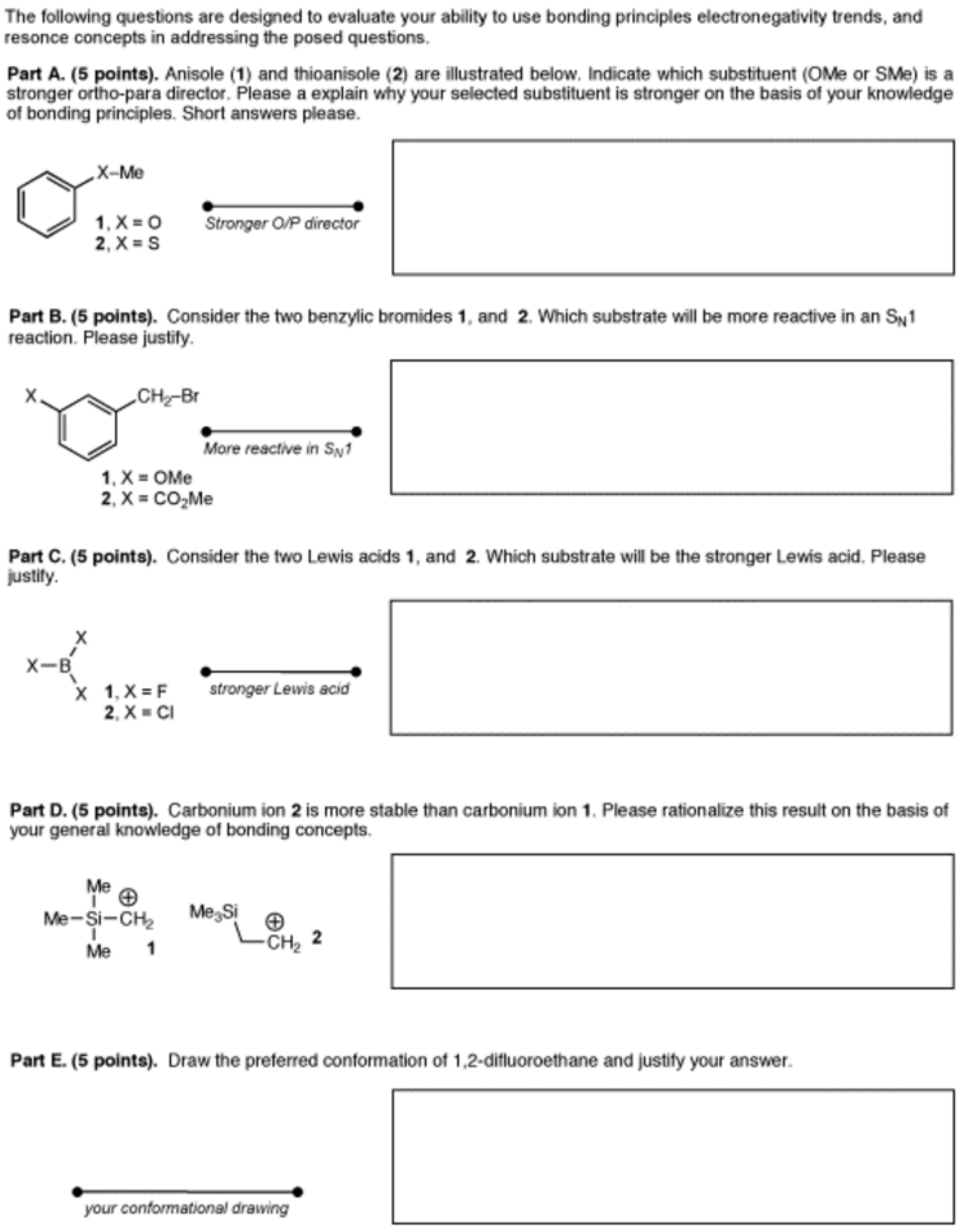
**Part C**



*Illustrate optimal reagent or sequence for this transformation*

## Problem 488

Contributer: **David A. Evans**
Citation:
Keywords: Reactivity quiz



The following questions are designed to evaluate your ability to use bonding principles electronegativity trends, and resonce concepts in addressing the posed questions.

**Part A. (5 points).** Anisole (**1**) and thioanisole (**2**) are illustrated below. Indicate which substituent (OMe or SMe) is a stronger ortho-para director. Please a explain why your selected substituent is stronger on the basis of your knowledge of bonding principles. Short answers please.

X–Me

**1**, X = O

**2**, X = S

*Stronger O/P director*

**Part B. (5 points).** Consider the two benzylic bromides **1**, and **2**. Which substrate will be more reactive in an $S_N1$ reaction. Please justify.

X, $CH_2$–Br

**1**, X = OMe

**2**, X = $CO_2Me$

*More reactive in $S_N1$*

**Part C. (5 points).** Consider the two Lewis acids **1**, and **2**. Which substrate will be the stronger Lewis acid. Please justify.

**1**, X = F

**2**, X = Cl

*stronger Lewis acid*

**Part D. (5 points).** Carbonium ion **2** is more stable than carbonium ion **1**. Please rationalize this result on the basis of your general knowledge of bonding concepts.

**1**

**2**

**Part E. (5 points).** Draw the preferred conformation of 1,2-difluoroethane and justify your answer.

*your conformational drawing*

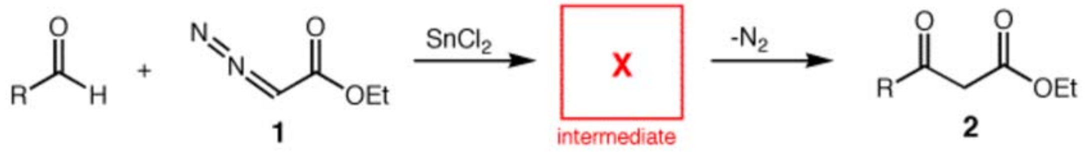
## Problem 503

Contributer: **David A. Evans**

Citation:

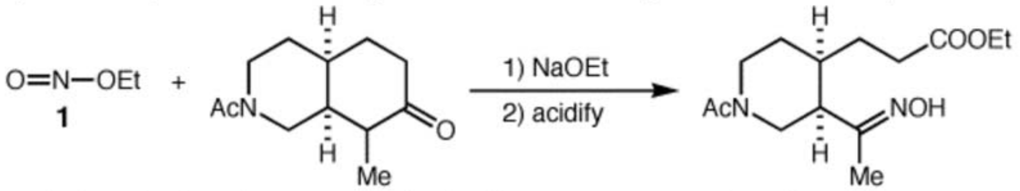
Keywords: Mechanism quiz

**Question 5 (10 points)**. Ethyl diazoacetate (**1**), under the influence of the Lewis acid catalyst $SnCl_2$, catalyzes the illustrated reaction to form the keto-ester **2**.



Write out a detailed mechanism which accounts for the illustrated transformation. Provide your answer in the space provided below. *In your mechanism, clearly box in the probable structure of X.*

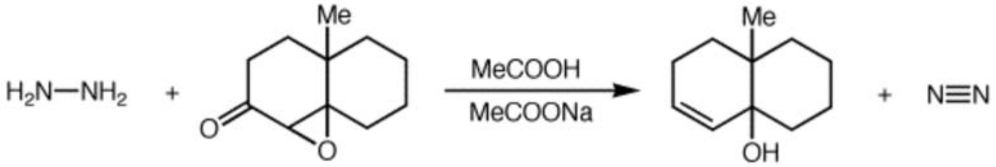
**Question 6 (10 points)**. The interesting fragmentation reaction illustrated below can be found in the first successful synthesis of quinine carried out by Woodward and Doering on the Harvard campus in 1945.



Write out a detailed mechanism which accounts for the illustrated transformation. Provide your answer in the space provided below. *Hint: Consider the reactions of ethyl nitrite (**1**) to be analogous to the reactions of a conventional carboxylic acid ester.*

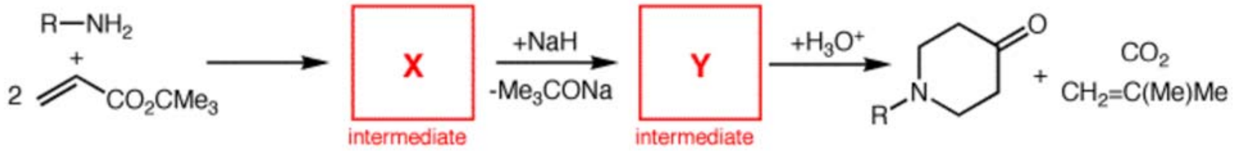
**Problem 504** Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz

**Question 7 (10 points)**. The reaction shown below is referred to as the **Wharton Rearrangement.**



Write out a detailed mechanism which accounts for the illustrated transformation. Provide your answer in the space provided below.

**Question 8 (10 points)**. The reaction shown below provides a convenient approach to the synthesis of the illustrated aza-ketone.

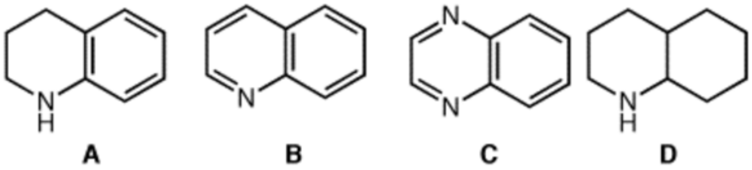


Write out a detailed mechanism which accounts for the illustrated transformation. Provide your answer in the space provided below. *In your mechanism, clearly box in the probable structures of X & Y.*

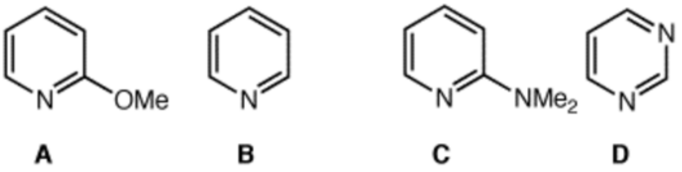
**Problem 508** Contributer: **David A. Evans**
Citation:
Keywords: Reactivity quiz

**Question 15 (20 points).** In the two questions below you are asked to rank the relative strengths of the series of illustrasted acids and bases. Use your knowledge of resonance and inductive effects to answer this question.

**Part A: (10 points)** For the series of bases shown below, rank the set from strongest to weakest.

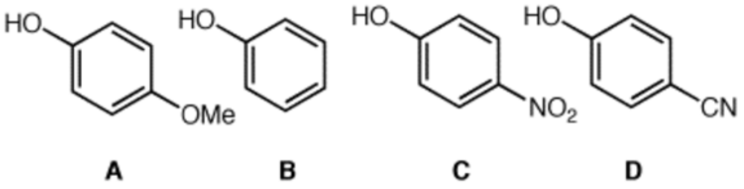


——Strongest
——
——
——weakest

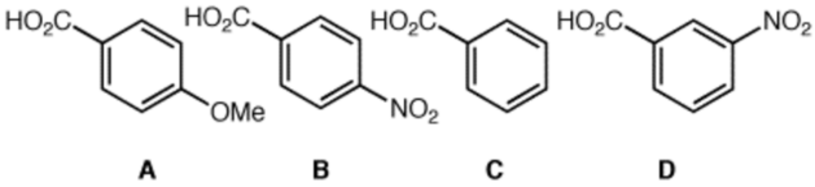


——Strongest
——
——
——weakest

**Part B: (10 points)** For the series of acids shown below, rank the set from strongest to weakest.



——Strongest
——
——
——weakest

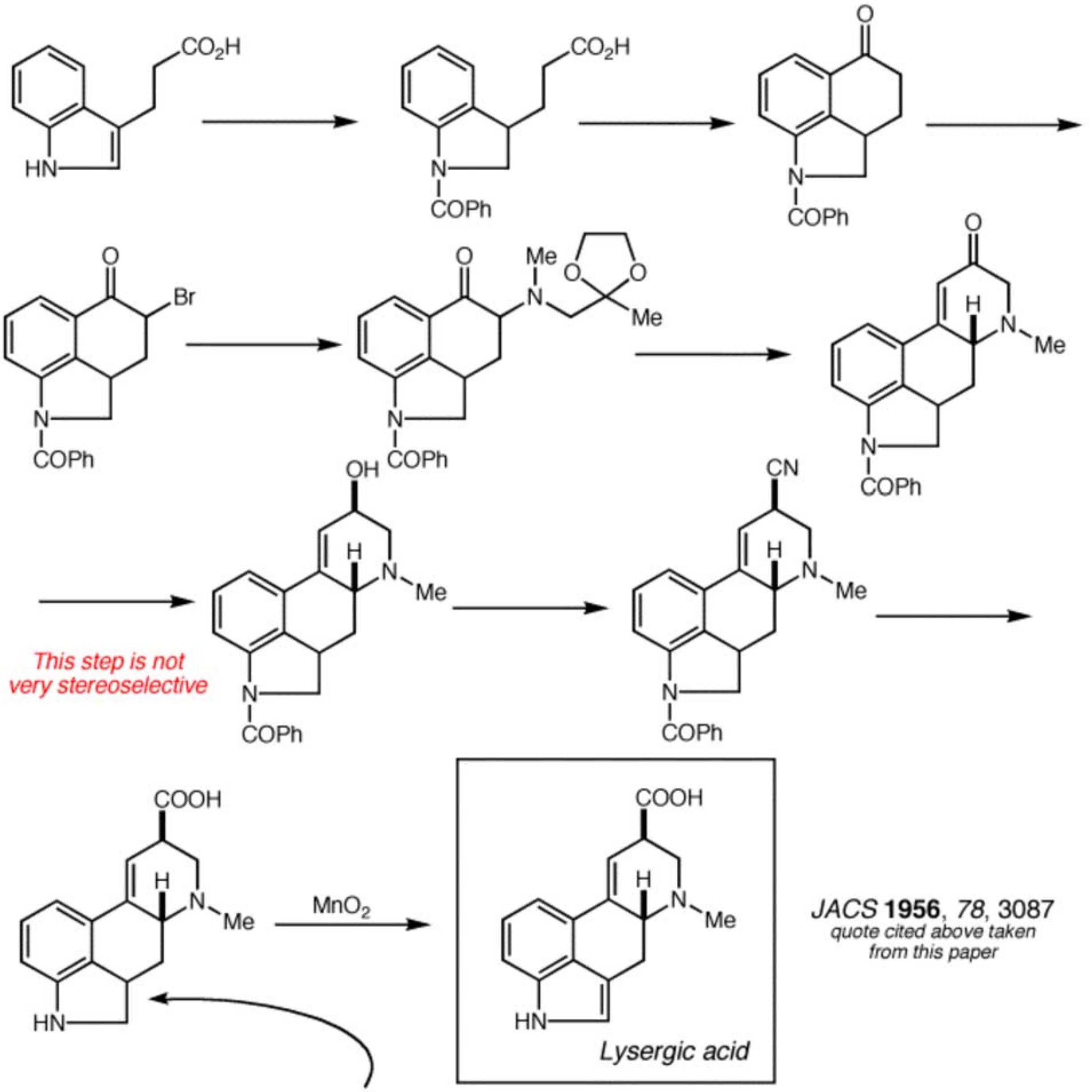


——Strongest
——
——
——weakest

## Problem 510

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1956**, *78*, 3087
Keywords: Reaction quiz

**Question 17 (30 points).** "The striking physiological properties of ergot early directed attention to this remarkable product of the growth of the fungus *Claviceps purpurea* on rye grain. Pre-Christian allusions to its effects have been recorded, and it was identified in 1676 as the causative agent of the dreaded medieval scourge, St. Anthony's Fire." Subsequent research has ultimately documented that no less than six amides of lysergic acid are produced by this fungus. The key intermediates in the first synthesis of lysergic acid, accomplished in 1956, are shown below. Using your knowledge of organic reactions fill in the reagents required to execute the illustrated transformations over each arrow. If several steps are required, label them as 1), 2) etc.



*This step is not very stereoselective*

*Lysergic acid*

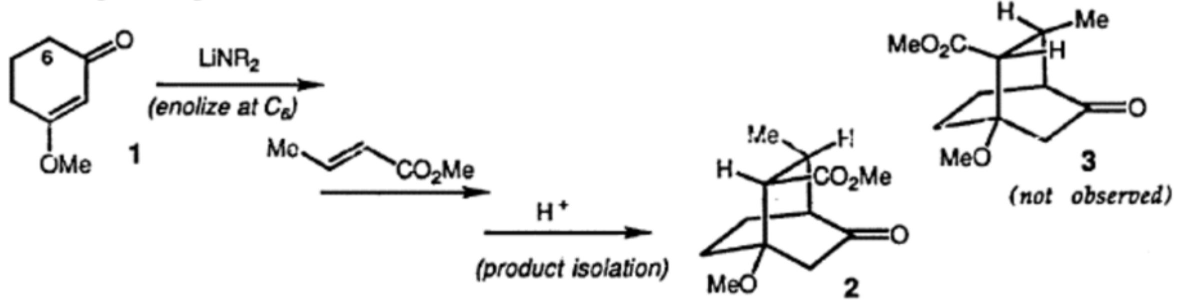
*JACS* **1956**, *78*, 3087
*quote cited above taken from this paper*

*Note: The double bond in this position must be removed in the initial stages of the synthesis to avoid unwanted side reactions in the Friedel-Crafts cyclization step.*

**Problem 518**

Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz

**Question 4 (10 points).** When ketone 1 is enolized with a strong amide base and treated with methyl crotonate the bicyclic ketone 2 is obtained in good yield after a conventional isolation procedure. It is of considerable interest that the other possible product diastereomer 3 is not observed.

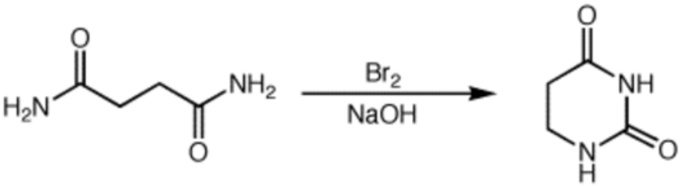


Write out a detailed mechanism which accounts for the illustrated transformation. Provide your answer in the space below. In outlining this transformation draw intermediates but not transition states.

## Problem 519

Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz

**Question 5 (10 points)**. When the illustrated amide is treated with bromine under basic conditions the following transformation takes place.

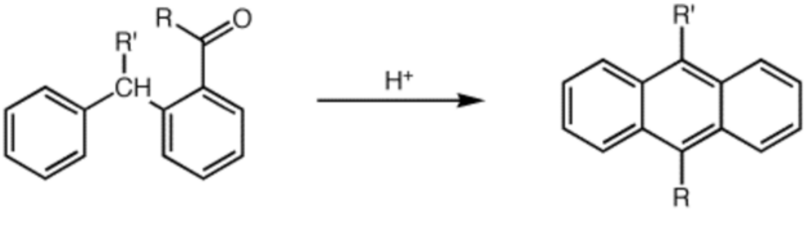


Write out a detailed mechanism which accounts for this transformation in the space provided below. In outlining this transformation draw intermediates but not transition states.

## Problem 520

Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz

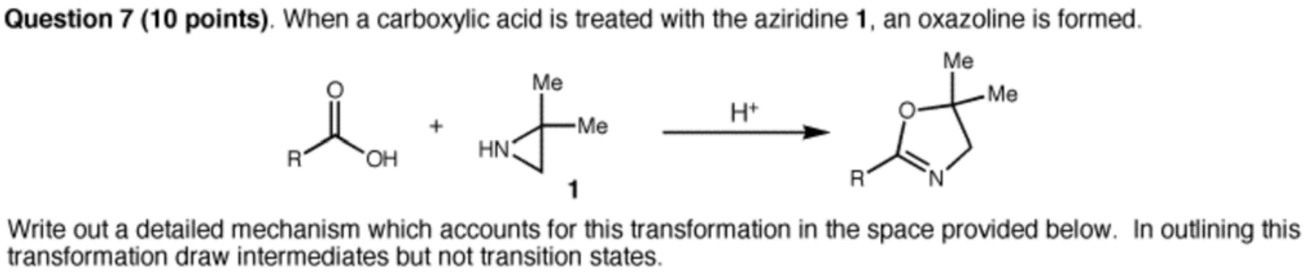
**Question 6 (10 points)**. When the illustrated reactant is treated with acid, the following transformation takes place.



Write out a detailed mechanism which accounts for the illustrated transformation. Provide your answer in the space below. In outlining this transformation draw intermediates but not transition states.

## Problem 521

Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz



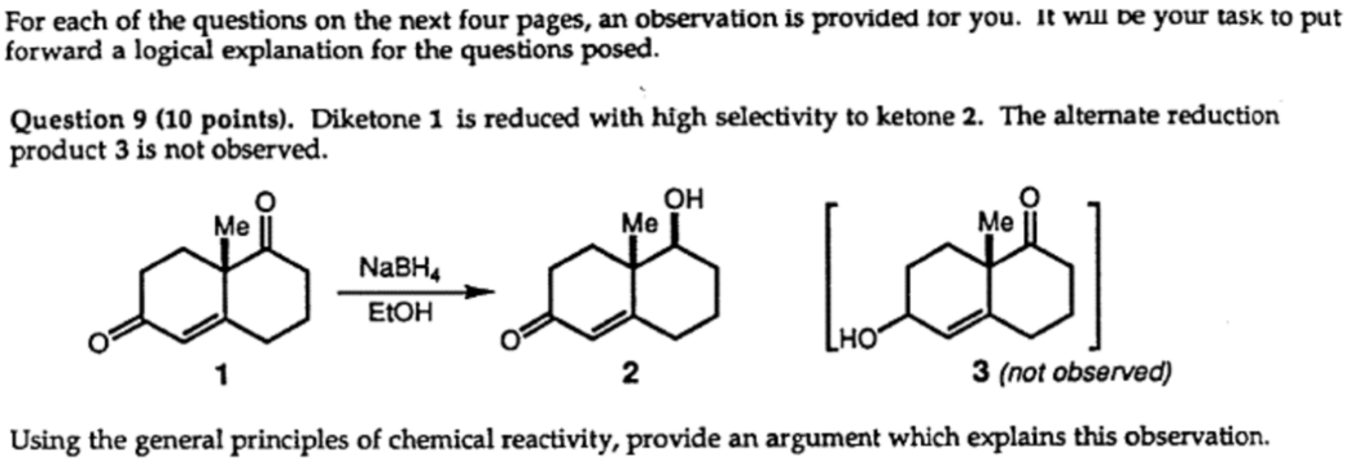
**Question 7 (10 points)**. When a carboxylic acid is treated with the aziridine **1**, an oxazoline is formed.

O
R
OH
+
Me
Me
HN
1
H+
Me
Me
O
R
N

Write out a detailed mechanism which accounts for this transformation in the space provided below. In outlining this transformation draw intermediates but not transition states.

## Problem 523

Contributer: **David A. Evans**
Citation:
Keywords: Reactivity quiz



For each of the questions on the next four pages, an observation is provided for you. It will be your task to put forward a logical explanation for the questions posed.

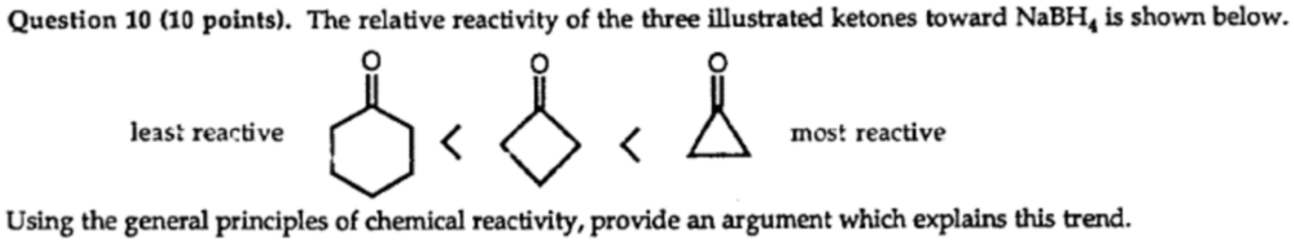
**Question 9 (10 points). Diketone 1 is reduced with high selectivity to ketone 2. The alternate reduction product 3 is not observed.**

Me
O
O
1
NaBH₄
EtOH
Me
OH
O
2
Me
O
HO
3 (not observed)

Using the general principles of chemical reactivity, provide an argument which explains this observation.

## Problem 524

Contributer: **David A. Evans**
Citation:
Keywords: Reactivity quiz



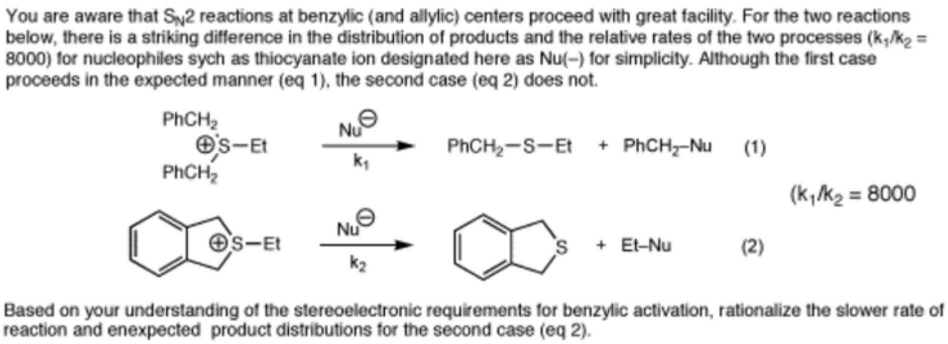
**Question 10 (10 points). The relative reactivity of the three illustrated ketones toward $NaBH_4$ is shown below.**

least reactive
<
<
most reactive

Using the general principles of chemical reactivity, provide an argument which explains this trend.

## Problem 526

Contributer: **David A. Evans**
Citation:
Keywords: Reactivity quiz

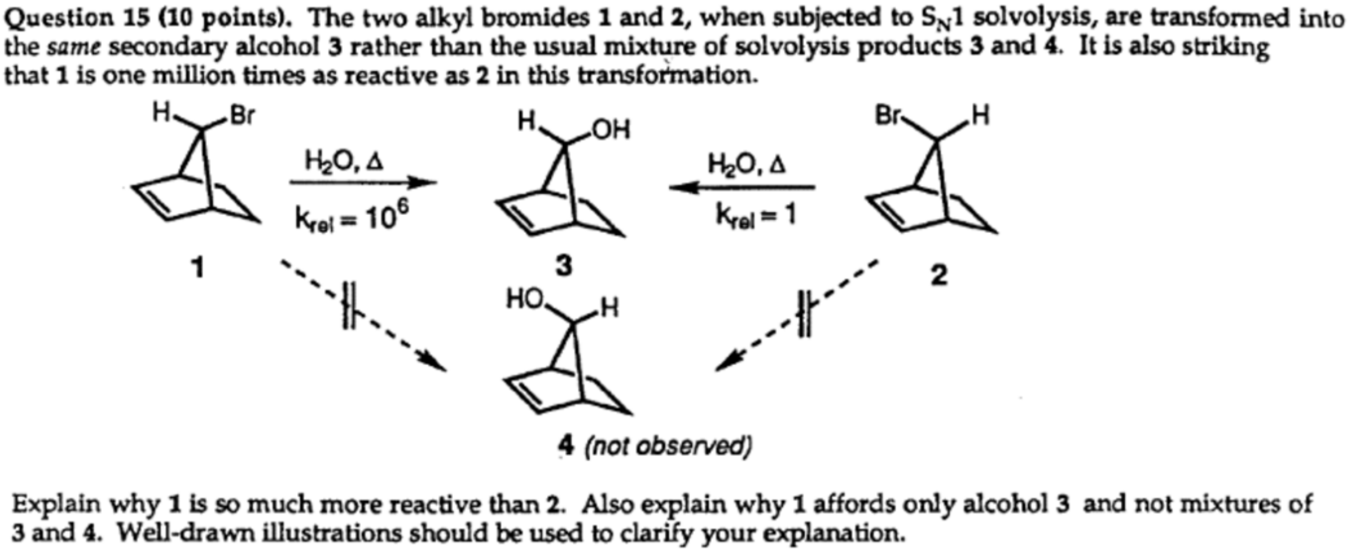


You are aware that $S_N2$ reactions at benzylic (and allylic) centers proceed with great facility. For the two reactions below, there is a striking difference in the distribution of products and the relative rates of the two processes ($k_1/k_2$ = 8000) for nucleophiles sych as thiocyanate ion designated here as Nu(–) for simplicity. Although the first case proceeds in the expected manner (eq 1), the second case (eq 2) does not.

Based on your understanding of the stereoelectronic requirements for benzylic activation, rationalize the slower rate of reaction and enexpected product distributions for the second case (eq 2).

## Problem 529

Contributer: **David A. Evans**
Citation:
Keywords: Reactivity quiz



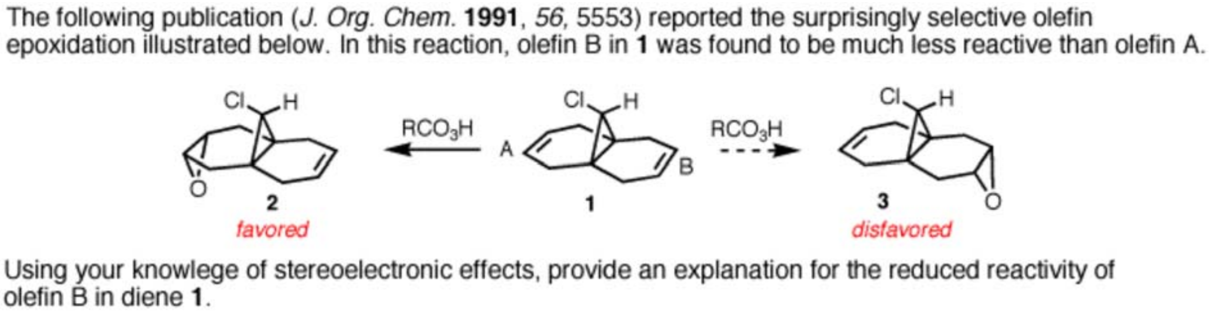
**Question 15 (10 points). The two alkyl bromides 1 and 2, when subjected to $S_N1$ solvolysis, are transformed into the *same* secondary alcohol 3 rather than the usual mixture of solvolysis products 3 and 4. It is also striking that 1 is one million times as reactive as 2 in this transformation.**

H
Br
H2O, Δ
krel = 10^6
H
OH
H2O, Δ
krel = 1
Br
H
1
3
2
HO
H
4 (not observed)

**Explain why 1 is so much more reactive than 2. Also explain why 1 affords only alcohol 3 and not mixtures of 3 and 4. Well-drawn illustrations should be used to clarify your explanation.**

## Problem 530

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1991**, *56*, 5553
Keywords: Reactivity quiz



The following publication (*J. Org. Chem.* **1991**, *56*, 5553) reported the surprisingly selective olefin epoxidation illustrated below. In this reaction, olefin B in **1** was found to be much less reactive than olefin A.

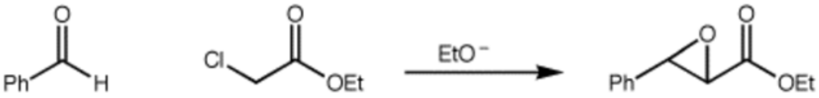
Cl
H
RCO3H
A
Cl
H
B
RCO3H
Cl
H
O
2
favored
1
3
O
disfavored

Using your knowlege of stereoelectronic effects, provide an explanation for the reduced reactivity of olefin B in diene **1**.

## Problem 538

Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz

**Question 1 (15 points)**. When the illustrated reactants are treated with a strong base such as ethoxide the following transformation takes place.

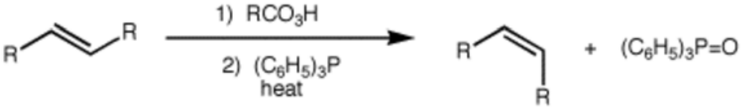


Write out a detailed mechanism which accounts for this transformation in the space provided below. In outlining this transformation draw intermediates but not transition states.

## Problem 539

Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz

**Question 2 (15 points).** You have recently been introduced to the **Wittig Reaction** and are now becoming familiar with its utility in synthesis. You have also been introduced to some of the mechanistic details of this process. We now present you with the reaction illustrated below, also based on phorphorus, which you have not yet seen. In this two-step process, trans and cis olefins may be stereospecifically interconverted.

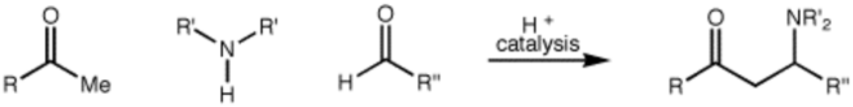


Write out a detailed mechanism which accounts for this transformation in the space provided below. In outlining this transformation draw intermediates but not transition states.

## Problem 540

Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz

**Question 3 (15 points)**. The process shown below is called the **Mannich Condensation**. This reaction frequently appears as a key step in the biosynthesis of alkaloids, natural products which contain basic nitrogen. The important structural feature in the target structure which suggests the Mannich transform is the presence of a 1,3 nitrogen-oxygen relationship.



**There are two well-differentiated mechanistic pathways that lead from starting materials to product. The two mechanisms differ in the sequence of assemblage of the reaction constituents.**

Write out both detailed mechanisms (A & B) which account for this transformation in the space provided below. In outlining this transformation draw intermediates but not transition states.

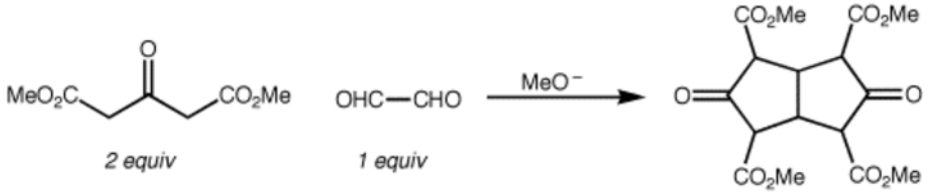
**Mechanism A: (8 points)**

**Mechanism A: (7 points)**

## Problem 541

Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz

**Question 4 (15 points)**. When the illustrated reactants are treated with a strong base such as methoxide the following transformation takes place.

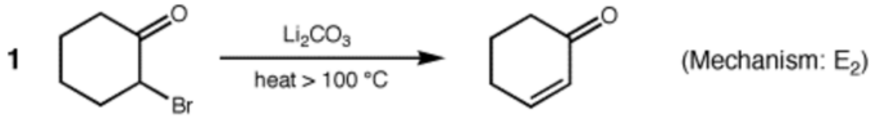


Write out a detailed mechanism which accounts for this transformation in the space provided below. In outlining this transformation draw intermediates but not transition states.

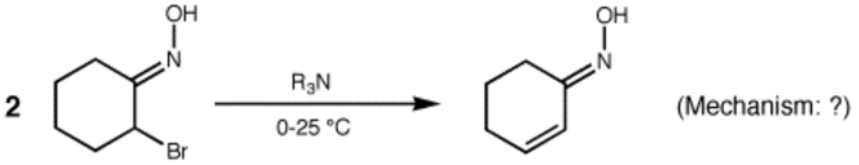
## Problem 542

Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz

**Question 5 (15 points)**. The base promoted elimination of 2-bromo ketones such as **1** follows a traditional E$_2$ mechanism at elevated temperatures.



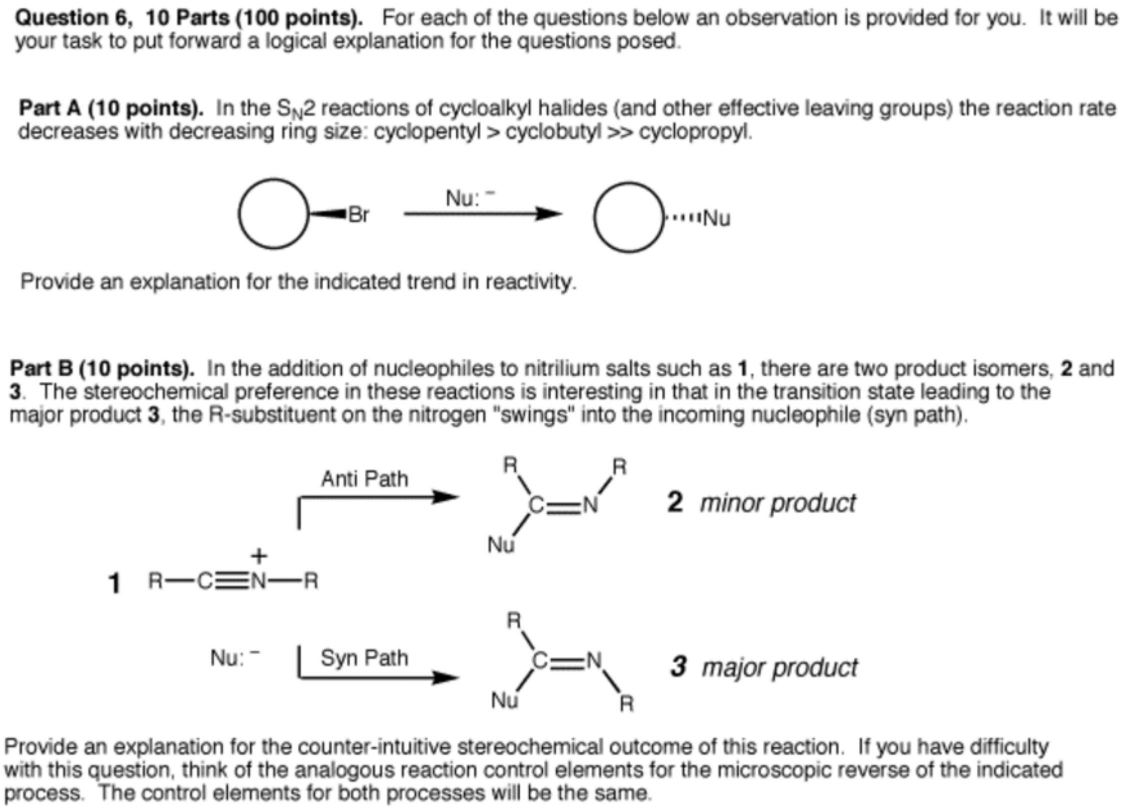
In contrast, the dehydrohalogenation of the derived oxime **2** occurs under very mild conditions. The use of oximes (and hydrazones) in these types of reactions forms the basis of a general strategy for the mild dehydrohalogenation of 2-halo ketones introduced by **Mattox and Kendall**.
*One piece of information which is relevant to the mechanism is that the unprotected oxime OH is required for facile elimination.*



Write out a detailed mechanism which accounts for this transformation in the space provided below. In outlining this transformation draw intermediates but not transition states.

## Problem 543

Contributer: **David A. Evans**
Citation:
Keywords: Reactivity quiz



**Question 6, 10 Parts (100 points).** For each of the questions below an observation is provided for you. It will be your task to put forward a logical explanation for the questions posed.

**Part A (10 points).** In the $S_N2$ reactions of cycloalkyl halides (and other effective leaving groups) the reaction rate decreases with decreasing ring size: cyclopentyl > cyclobutyl >> cyclopropyl.

Provide an explanation for the indicated trend in reactivity.

**Part B (10 points).** In the addition of nucleophiles to nitrilium salts such as **1**, there are two product isomers, **2** and **3**. The stereochemical preference in these reactions is interesting in that in the transition state leading to the major product **3**, the R-substituent on the nitrogen "swings" into the incoming nucleophile (syn path).

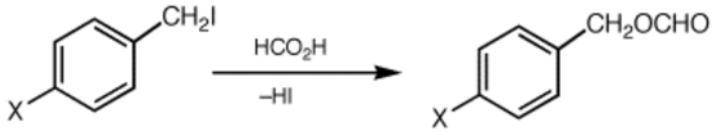
Provide an explanation for the counter-intuitive stereochemical outcome of this reaction. If you have difficulty with this question, think of the analogous reaction control elements for the microscopic reverse of the indicated process. The control elements for both processes will be the same.

## Problem 558

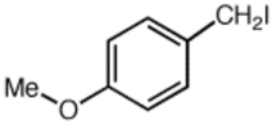
Contributer: **David A. Evans**
Citation:
Keywords: Reactivity quiz

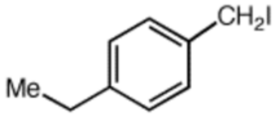
In each of the questions provided below, the reaction is influenced in some way by resonance effects. Using your knowledge of resonance and induction, predict the order of reactivity of the triads of substrates provided below.

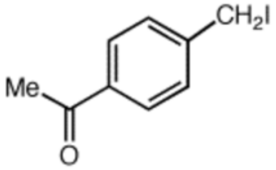
**Part A (6 points).** Consider the $S_N1$ reaction of the following substituted benzyl halides in formic acid.



Predict the order of reactivity of the three substrates shown below: **Reactivity Order: 1 (fastest) fi 3 (slowest).**



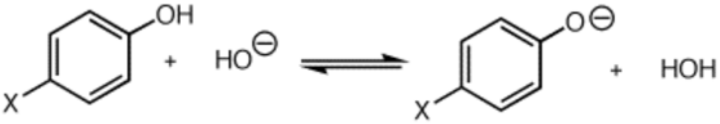




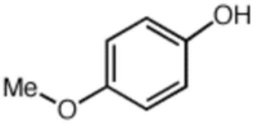
**Reactivity Order:** ______ ______ ______

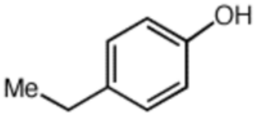
**Part B (4 points).**
Take the most reactive substrate in Part A above and draw the significant resonance structures which contribute to the stablity of the derived intermediate carbonium ion.

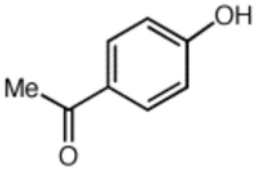
**Part C (6 points).** Consider the acid-base reaction of the substituted phenols below with aqueous hydroxide:



Predict the acidity order for the three phenols shown below: **Acidity Order: 1 (most) fi 3 (least).**







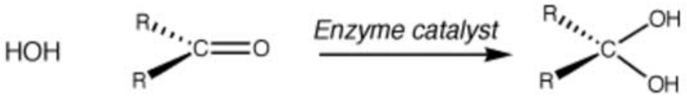
**Acidity Order:** ______ ______ ______

**Part D (4 points).**
Take the most acidic substrate in Part C above and draw the significant resonance structures which contribute to the stability of the derived conjugate base.

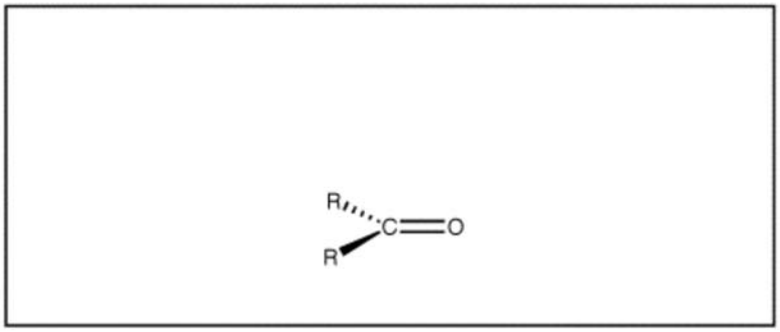
## Problem 568

Contributer: **David A. Evans**
Citation:
Keywords: Reactivity quiz

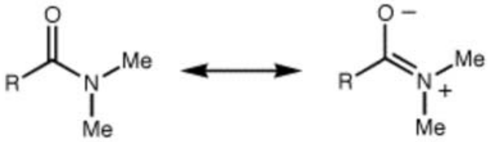
**Part A (10 points).** *The reaction illustrated below is catalyzed by an enzyme which you will build.* In answering this question you are requested to design an environment containing those functional groups that will *best* promote this addition reaction. Keep in mind that the "catalytic" groups in the active site of an enzyme occupy a fixed position in space; *Hence spacial orientation is of considerable importance as a design consideration.*



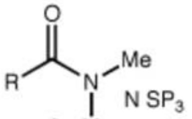
In the space provided, place the reactants in their optimal geometries for undergoing reaction and add those catalytic functional groups which you feel will best promote the rate of addition.



**Part B (10 points).** The reactivity of the amide C=O group is dominated by its resonance interaction with the attached nitrogen which, although more electronegative than carbon, reduces C=O electrophilicity.

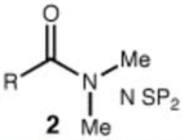


**(5 points).** Presume that you have the three amides shown below. Amide **2** contains a "normal" nitrogen as found in a "garden-variety"; Amide **1** contains a nitrogen which is SP3 hydridized; finally, amide **3** has been rotated 90 ° about the C(acyl)–N bond. Predict the reactivity order of these 3 substrates toward basic hydrolysis. *Circle the correct adjective under each substrate.*



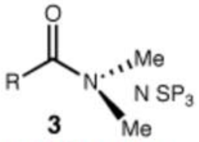
**1**

**Reactivity order:**
most
intermediate
least



**2**

**Reactivity order:**
most
intermediate
least



**3**

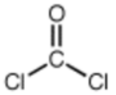
**Reactivity order:**
most
intermediate
least

**(5 points).** Provide the reasoning which led you to predict the above reactivity order.

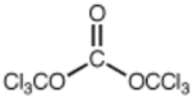
## Problem 570

Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz

Phosgene (**1**) is a useful reagent in synthesis that is, unfortunately a highly toxic substance (It was used in WW-I as a poison gas). Triphosgene (**2**), a formal trimer of **1**, is a crystalline solid that is safer and easier to handle. Recently, triphosgene has been used widely as a phosgene replacement in many reactions.

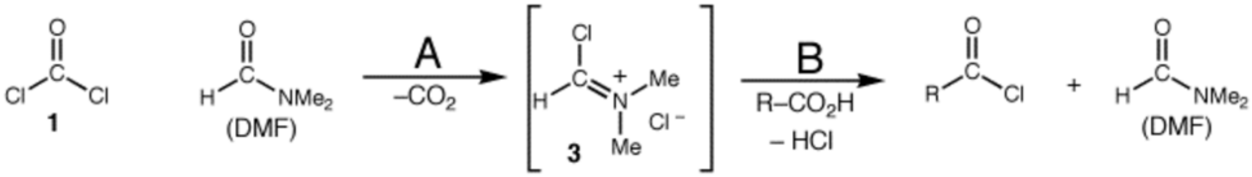


**Phosgene**
**1**



**Triphosgene**
**2**

**Part A (10 points).** Phosgene reacts with carboxylic acids, under dimethylformamide (DMF) catalysis, to form the acid chloride. In this reaction, DMF is transformed to an intermediate **3** which is involved in the overall transformation shown below:



**Propose a mechanism for Step A:**

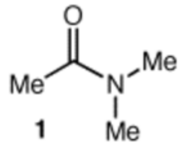
**Propose a mechanism for Step B:**

## Problem 574

Contributer: **David A. Evans**
Citation:
Keywords: Reactivity quiz

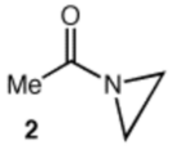
**Question 1 (20 points).** For each of the questions below and on the following page an observation is provided. Your task is to put forward a logical explanation for the questions posed. *The management appreciates concise answers. This bias will be reflected in grading your responses.*

**Part A. (5 points).** The IR carbonyl stretching frequency of dimethyl acetamide (**1**) is 1660 cm$^{-1}$ while the carbonyl stretching frequency of the corresponding N-acyl aziridine (**2**) is 1700 cm$^{-1}$.



**1**

$\bar{\nu}$ C=O = 1660 cm$^{-1}$



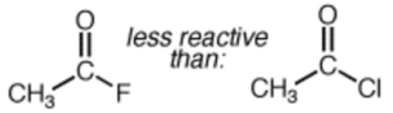
**2**

$\bar{\nu}$ C=O = 1700 cm$^{-1}$

Provide an explanation for the difference in the IR C=O frequencies of the two compounds.

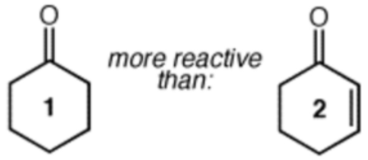
**Part B (5 points).** In an apparent paradox, acid fluorides are less reactive acylating agents than acid chlorides.

Provide an explanation (rationalization) for this observation.



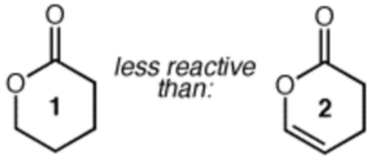
**Part C (5 points).** Cyclohexanone (**1**) is approximately ten times as reactive toward Grignard and hydride nucleophiles than cyclohexenone (**2**).

Provide an explanation for the observed greater reactivity of **1** toward nucleophiles.



**Part C (5 points).** Valerolactone (**1**) is less reactive toward nucleophilic addition than the corresponding unsaturated lactone **2**.

Provide an explanation for the observed greater reactivity of **1** toward nucleophiles.

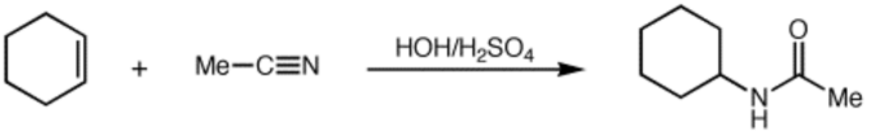


## Problem 575

Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz

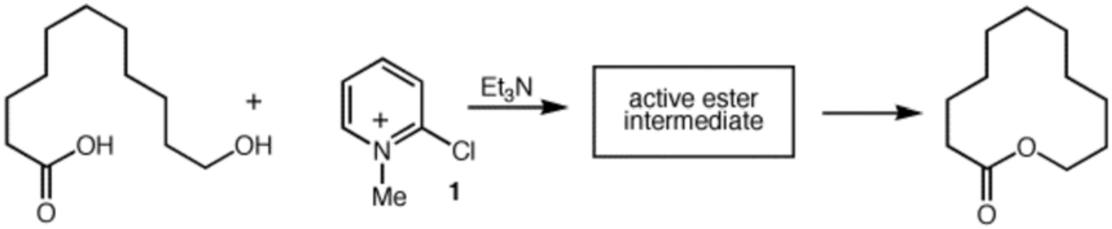
**Question 2 (35 points).** This question consists of 5 parts (7 pts each) on this and the following page. In each question you are asked to provide a reasonable mechanism for the particular transformation illustrated.

**Part A (7 points).** When the illustrated reactants are treated with strong aqueous acid the following transformation takes place: This reaction is called the Ritter Reaction.



Write out a detailed mechanism which accounts for this transformation in the space provided below. In describing this transformation draw intermediates but not transition states.

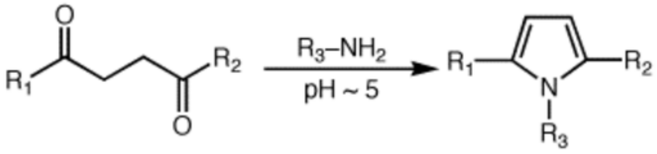
**Part B (7 points).** 2-Halopyridinium salts such as **1** may be employed to activate carboxyolic acids for ester and amide formation. The use of **1** in the formation of a 12-membered lactone is shown below



What is the structure of the **active ester intermediate** in the reaction of an acid, in the presence of an amine base, with **1**? Write out a detailed mechanism which accounts for this transformation in the space provided below. In describing this transformation draw intermediates but not transition states.

**Part C (7 points).** 1,4-diketones **1** and primary amines may be transformed into pyrroles **2** under the influence of an acid catalyst.

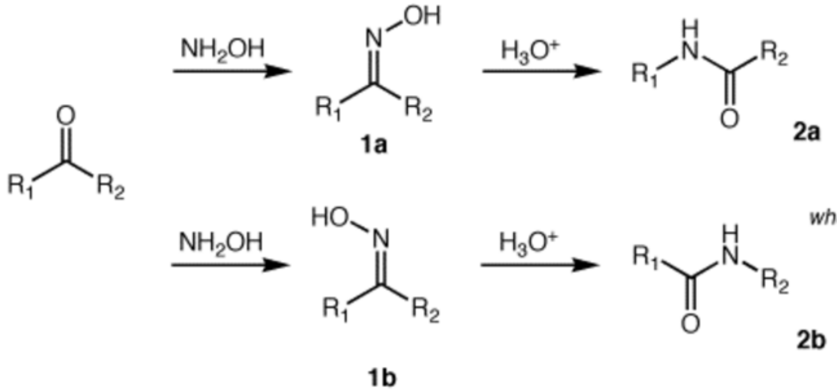
Write out a detailed mechanism which accounts for this transformation in the space provided below.



## Problem 576

Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz

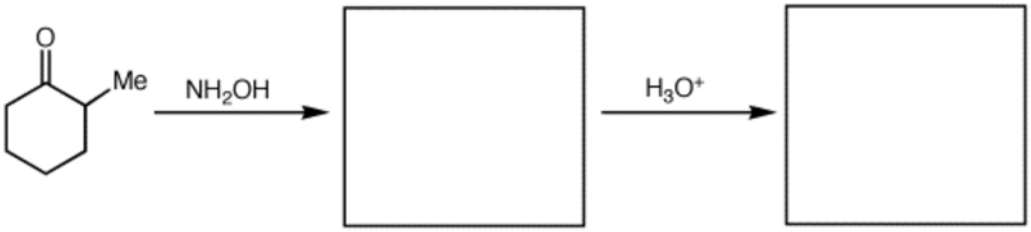
**Part D (7 points).** A very useful way to produce an amide from a ketone is through the acid-catalyzed rearrangement of the derived oxime isomers **1**. As illustrated, the structure of the amide product (**2a** or **2b**) is dictated by the stereochemistry of the oxime precursor (**1a** or **1b**).



*This transformation is complementary to the Baeyer-Villiger reaction wherein ketones are transformed into esters.*

Write out a detailed mechanism which accounts for the transformation of **1a** → **2a** in the space provided below. In describing this transformation draw intermediates but not transition states.

**Part E (7 points).** Predict the stereochemistry (see **1a** and **1b** above) of the major oxime product from the illustrated ketone and the structure of the derived amide product.



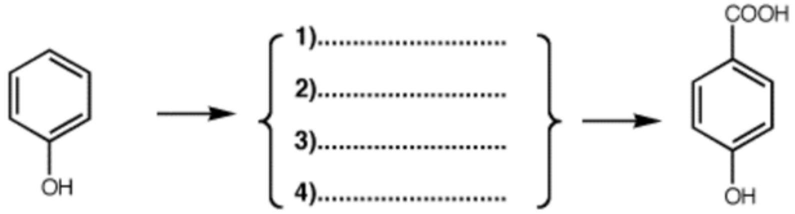
*provide your answers in the boxes*

## Problem 577

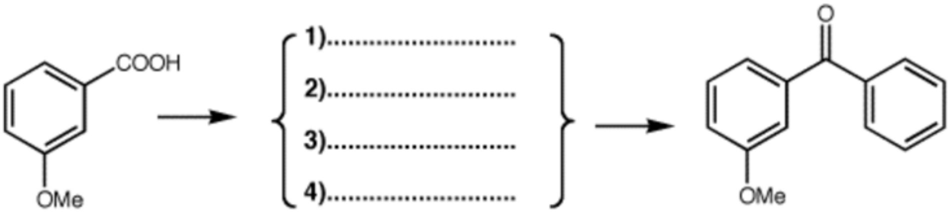
Contributer: **David A. Evans**
Citation:
Keywords: Reaction quiz

Each of the illustrated transformations may be carried out in no more than four steps. In answering this question it is important to define what is meant by "a step". In the context of this question "a step" will constitute a discrete chemical process which is initiated by the addition of a stoichiometric quantity of a given reagent or reagents. For example, the synthesis of an alcohol from a ketone and Grignard reagent is a two-step process: The addition step; and the neutralization step where the conjugate base of the alcohol is protonated with acid. Fill in the reagents (organic & inorganic) that are required to complete the synthesis exercise. You are free to use any additional organic molecules that might be required to complete the synthesis. *The efficiency of your reaction sequence will be evaluated.*

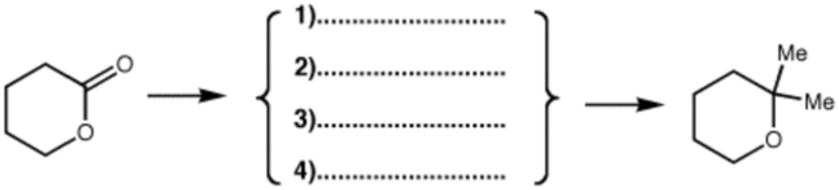
**(a)**
(5 points)



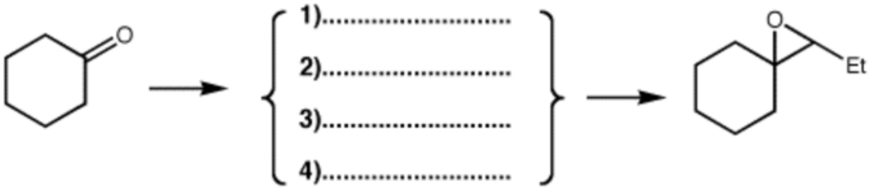
**(b)**
(5 points)



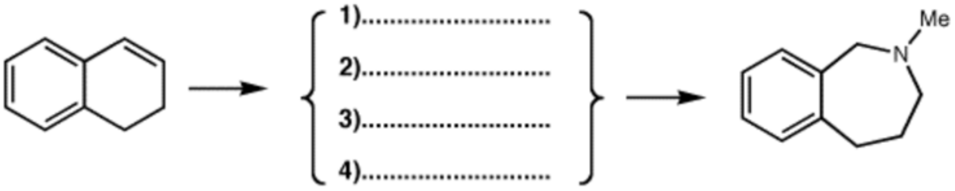
**(c)**
(5 points)



**(d)**
(5 points)



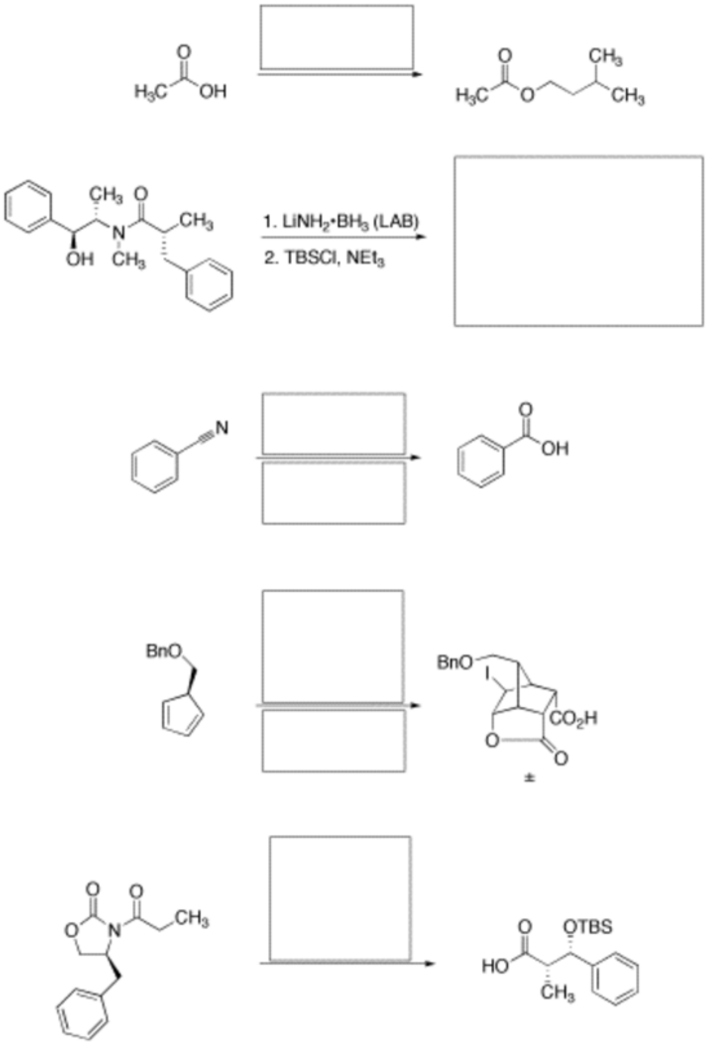
**(e)**
(5 points)



**Problem 583**

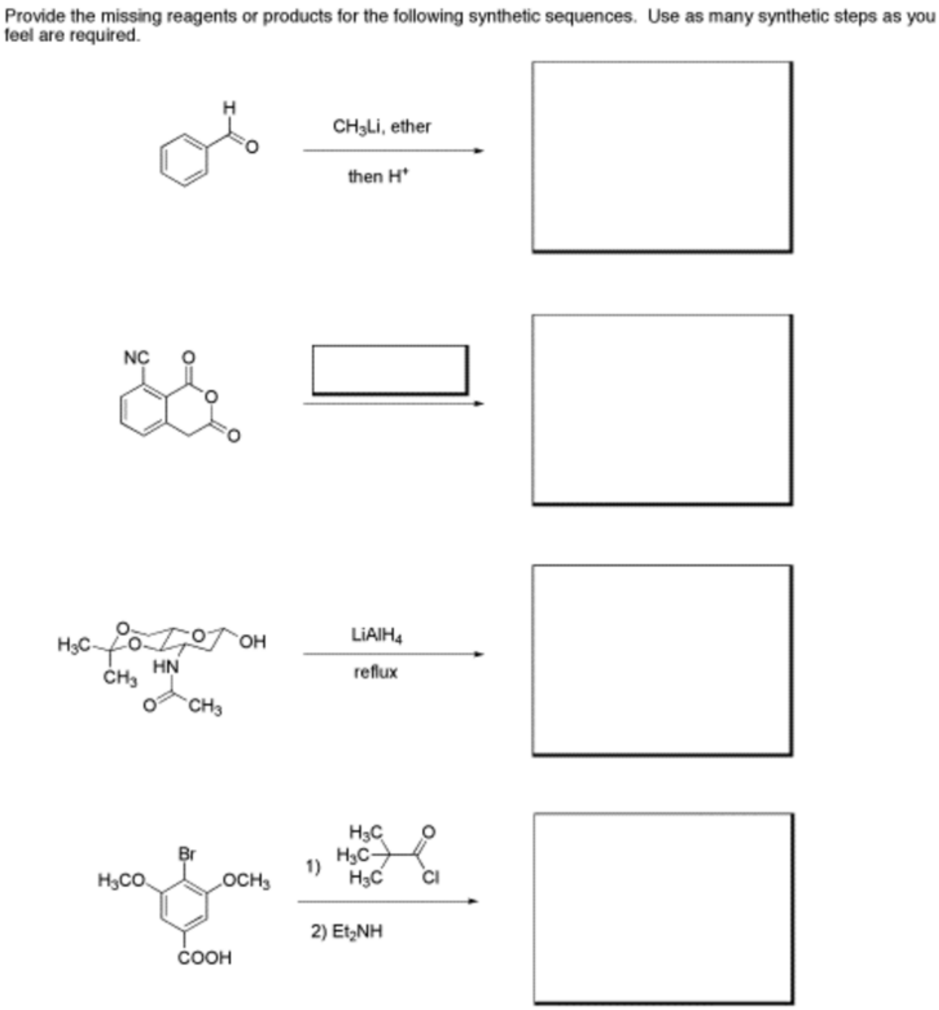
Contributer: **Christina White**
Citation:
Keywords: Reaction quiz

Provide the missing reagents or products for the following synthetic sequences. Use as many synthetic steps as you feel are required.



## Problem 584

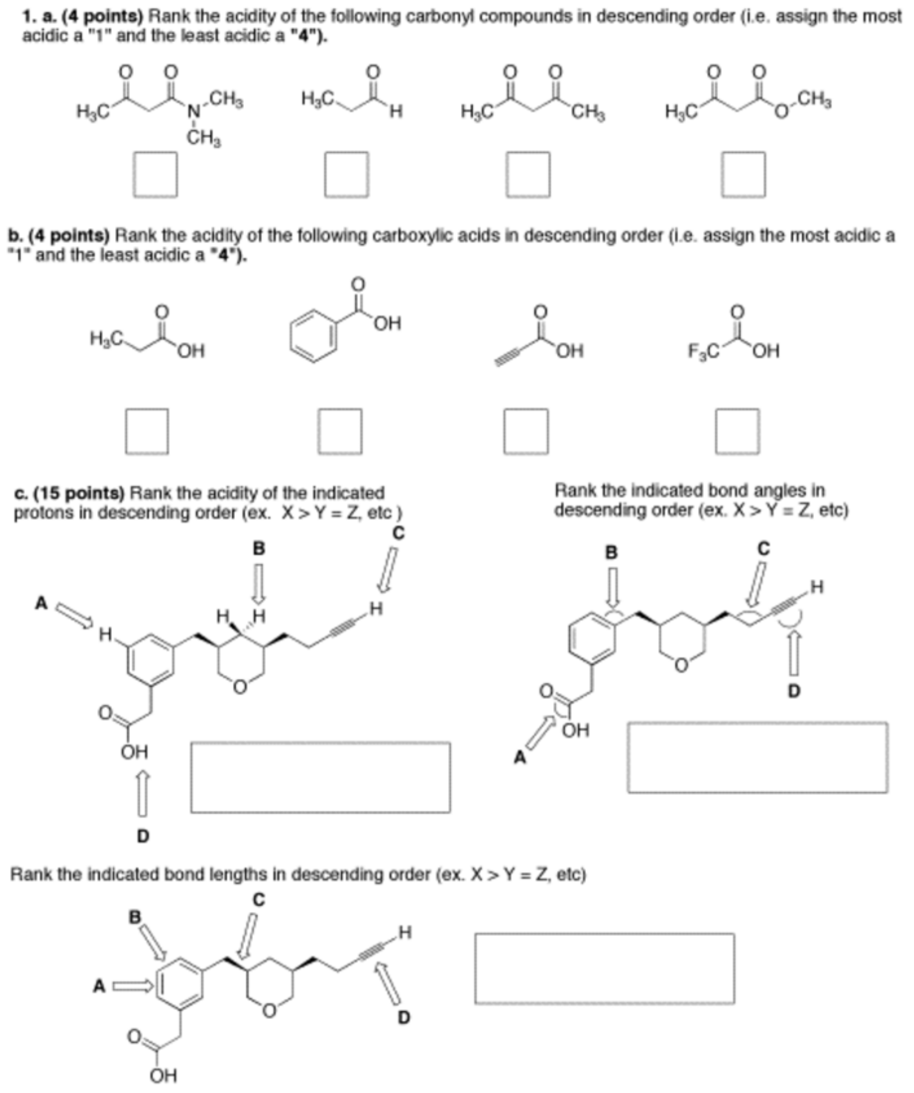
Contributer: **Christina White**
Citation:
Keywords: Reaction quiz



Provide the missing reagents or products for the following synthetic sequences. Use as many synthetic steps as you feel are required.

## Problem 585

| | |
|---|---|
| Contributer: | **Christina White** |
| Citation: | |
| Keywords: | Reactivity quiz |



**1. a. (4 points)** Rank the acidity of the following carbonyl compounds in descending order (i.e. assign the most acidic a "1" and the least acidic a **"4")**.

**b. (4 points)** Rank the acidity of the following carboxylic acids in descending order (i.e. assign the most acidic a "1" and the least acidic a **"4")**.

**c. (15 points)** Rank the acidity of the indicated protons in descending order (ex. X > Y = Z, etc )

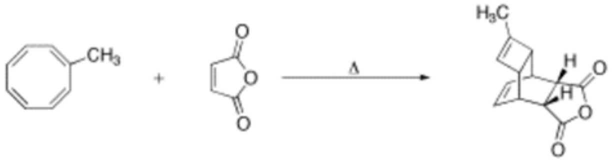
Rank the indicated bond angles in descending order (ex. X > Y = Z, etc)

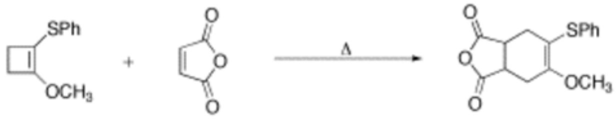
Rank the indicated bond lengths in descending order (ex. X > Y = Z, etc)

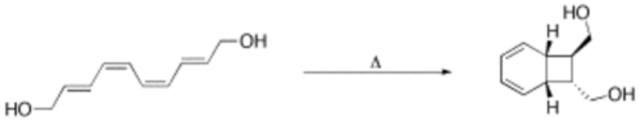
## Problem 586

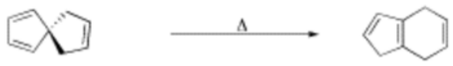
Contributer: **Christina White**
Citation:
Keywords: Reaction quiz

In the spaces provided, propose a mechanism for each of the reactions shown below. Be sure to fully classify any pericyclic reactions. Note that more than one step is required in each case.





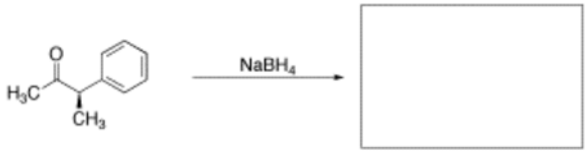


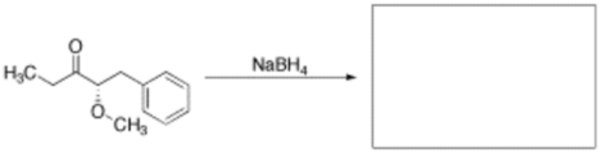


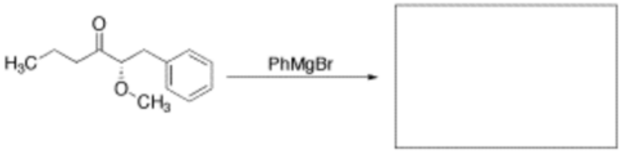
## Problem 587

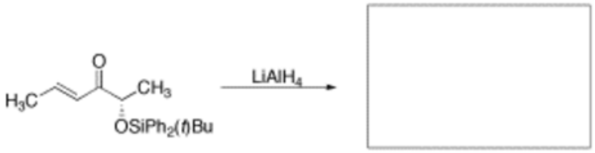
Contributer: **Christina White**
Citation:
Keywords: Reaction quiz

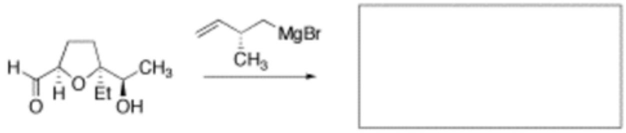
Indicate the products of each of the following carbonyl addition reactions. Briefly indicate the controlling element in each case (Felkin, chelate, etc.)







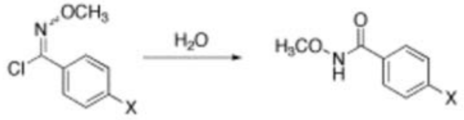




## Problem 588

Contributer: **Christina White**
Citation:
Keywords: Mechanism quiz

Johnson and coworkers at Texas Woman's University recently studied the hydrolysis of O methylbenzohydroximoyl chlorides



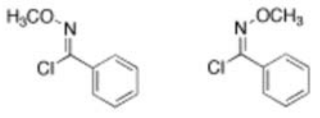
1

**a.** A Hammett plot analysis for the above reaction gives $\rho \sim -1.4$ (depending on what isomer of **1** is analyzed). Without even beginning to draw the specific mechanism, explain what *in general* the sign and magnitude of the slope say about this particular reaction's mechanism. Recall that Hammett LFERs are comparasions relative to the ionization of *p*-substitued benzoic acids. To jog your memory, the Hammett equation is shown below.

$$\log \frac{k_X}{k_H} = \rho\sigma_X$$

**b.** Propose an "arrow pushing" mechanism that is consistent with the Hammett data and your statement made in part "a"

**c.** The (Z)-isomer of **1** is about two orders of magnitude more reactive towards hydrolysis than the (E)-isomer. Drawing on your knowledge of molecular orbital theory, provide a rationale for this observation.



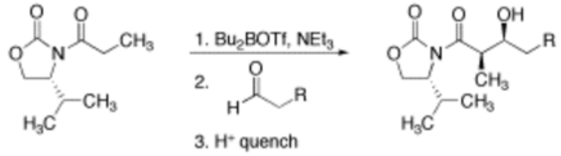
(*Z*)-**1** (*E*)-**1**

(more reactive)

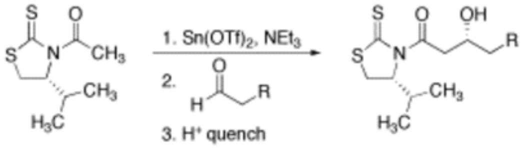
## Problem 589

Contributer: **Christina White**
Citation:
Keywords: Mechanism quiz

**a. (5 points)** The Evans asymmetric aldol reaction is one of the most dependable tools in the hands of synthetic chemists. Shown below is typical aldol reaction involving a propionimide and a generic aldehyde. The stereochemical outcome of this reaction is something that you are very familiar with at this point. Please draw a clear 3-dimensional representation of the Zimmerman-Traxler transition state that results in the product diastereomer shown.



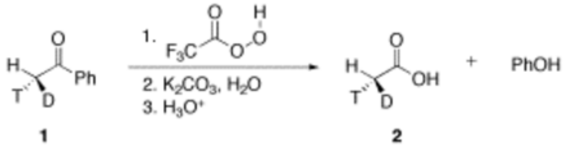
**b. (5 points)** The asymmetric acetate aldol reaction eluded synthetic chemists for many years. Nagao and coworkers developed the reaction shown below to provide one solution. The stereochemical outcome of the reaction is opposite of what you might expect based on what you know about the typical Zimmerman-Traxler transition state that is proposed to be active in the above reaction. Propose a Zimmerman-Traxler type transition state for the reaction shown below to justify the stereochemical outcome . It should be noted that unlike the boron Lewis acid used above, Sn(II) can have up to 4 ligands and is both oxo- and thiophilic.



## Problem 590

Contributer: **Christina White**
Citation:
Keywords: Mechanism quiz

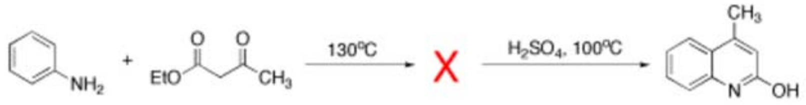
Isotope labeled natural products are useful tools in the hands of biochemists. For example, the ability to prepare D,T-labeled acetic acid, **2**, helped Cornforth and co-workers to investigate the mechanism of the malate synthase enzyme. The Baeyer-Villigar reaction can be used to prepare the desired labeled acetic acid (**2**) from ketone **1**. Propose a mechanism for this transformation.



## Problem 591

Contributer: **Christina White**
Citation:
Keywords: Mechanism quiz

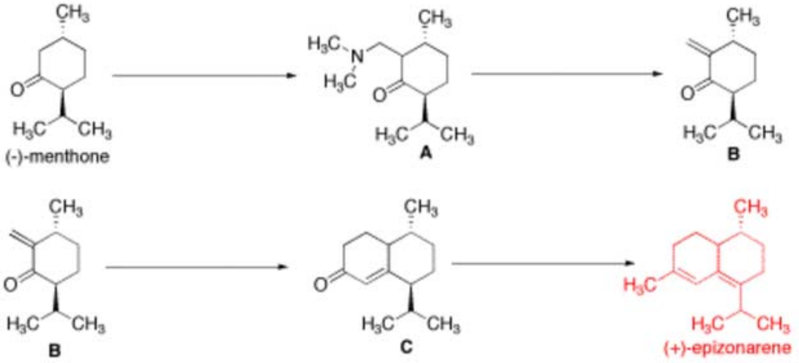
**7. (10 points)** Propose a mechanism for the two-step synthesis of quinoline from aniline and the following β-keto ester. Be sure to indicate which intermediate in your mechanism is intermediate X.



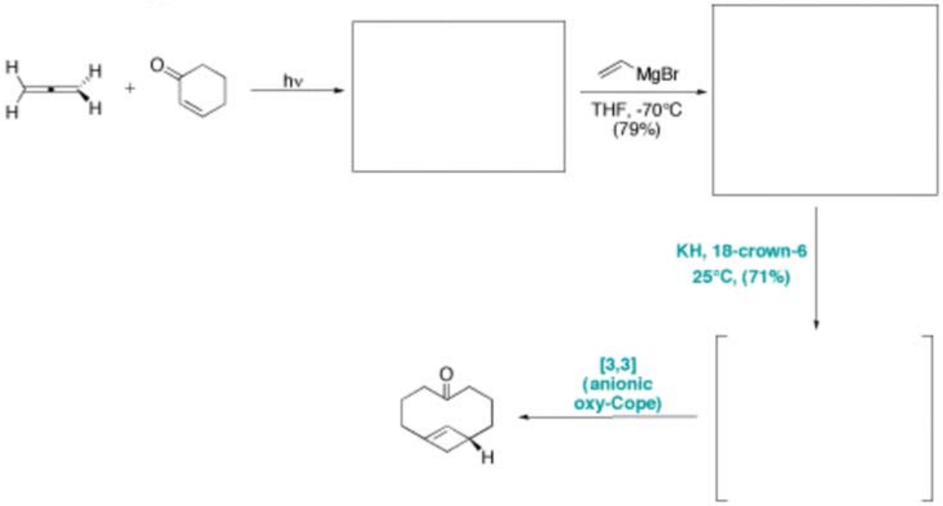
## Problem 592

Contributer: **Christina White**
Citation:
Keywords: Reaction quiz

**8. a. (10 points)** Plan out a synthesis of the natural product **(+)-epizonarene** via **A**-**C** starting from commercially available (-)-menthone by supplying the missing reagents. You do not have to use the same number of steps as indicated above and below the reaction arrows as long as your steps lead to the correct product.



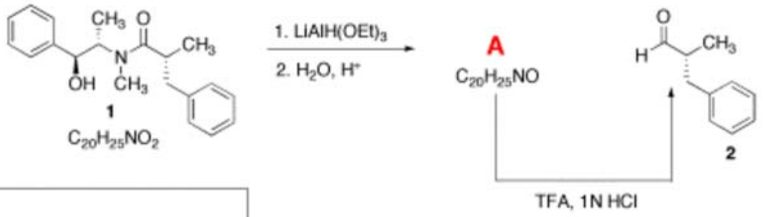
**b. (10 points)** The following synthetic sequence is taken from the Schreiber synthesis of the cockroach pheremone periplanone B. Please fill in the products resulting from each transformation. Include the relative stereochemistry in each product where applicable. (It is rumored that the students that worked on this project had a tough time keeping cockroaches at bay.)



## Problem 593

Contributer: **Christina White**
Citation:
Keywords: Mechanism quiz

**9. (15 points)** When pseudoephedrine amide **1** is reduced with lithium triethoxyaluminum hydride ($LiAlH(OEt)_3$) to access desired aldehyde **2**, even after a mild aqueous quench, a side product (**A**) is produced in addition to **2**. These common side products are easily converted to the desired aldehydes by aqueous treatment with a stronger acid such as trifluoroacetic acid (TFA). Given the formula for **A**, identify this side product.

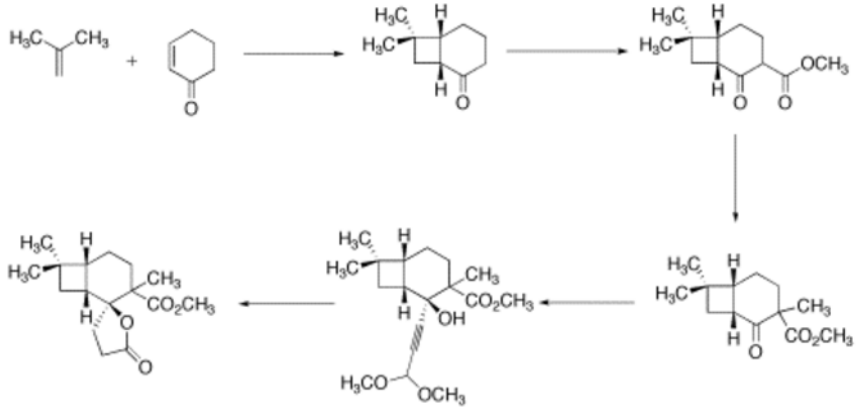


Using the space below, propose a mechanism for the transformation of **A** into desired product **2**. You need not explicitly indicate all proton tranfers (i.e. simply write proton transfer).

## Problem 595

Contributer: **Christina White**
Citation:
Keywords: Reaction quiz

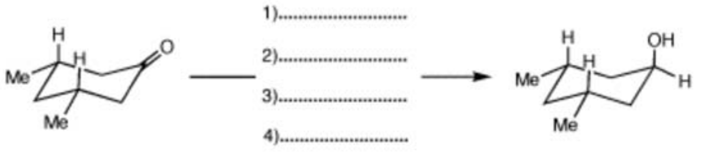
Fill in the missing reagents used in the synthetic sequence shown below. Use as many steps as you deem necessary. Be sure to indicate whether the first step is photochemical or thermal.

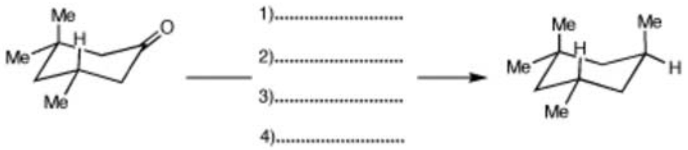


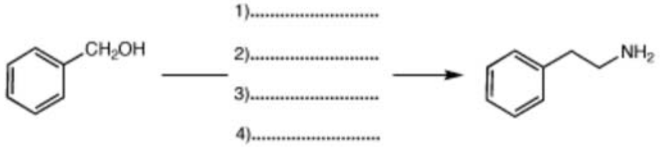
## Problem 598

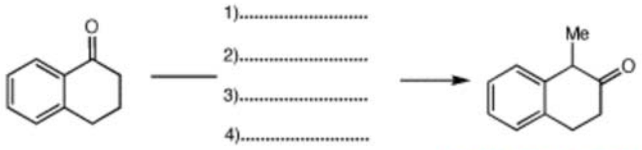
Contributer: **David A. Evans**
Citation:
Keywords: Reaction quiz

The transformations illustrated below may be completed in no more than 4 steps (excluding quenching or neutralization steps with water dilute acid or base). Write in the conditions necessary to complete these transformations. You will be graded on both the accuracy and efficiency of your proposed transformations. In other words, the shorter the number of proposed steps, the more favorably your answer will be viewed. Write the reagents required for the overall transformation in the spaces provided.









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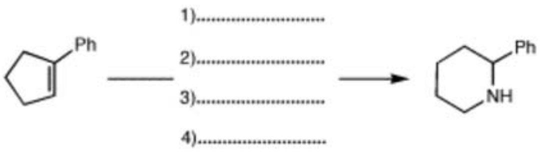
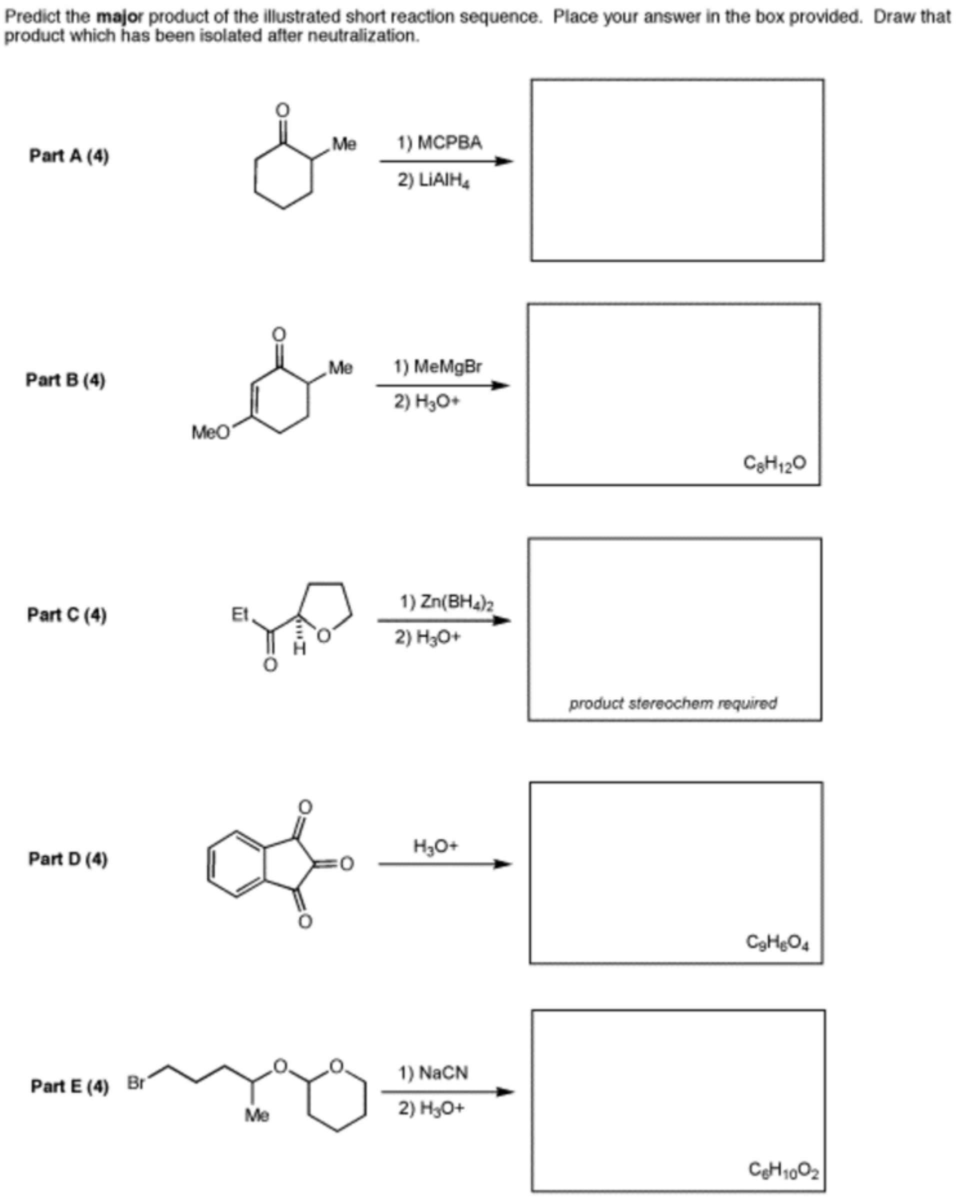


## Problem 599

Contributer: **David A. Evans**
Citation:
Keywords: Reaction quiz



Predict the **major** product of the illustrated short reaction sequence. Place your answer in the box provided. Draw that product which has been isolated after neutralization.

**Part A (4)**

**Part B (4)**

**Part C (4)**

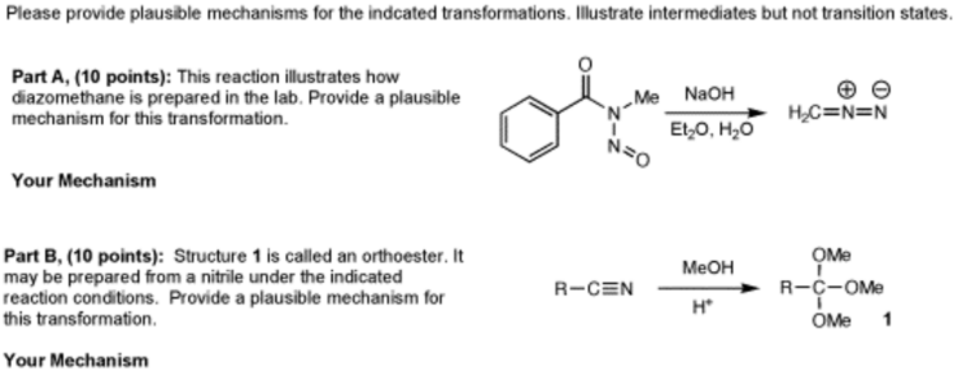
*product stereochem required*

**Part D (4)**

**Part E (4)**

## Problem 600

Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz



Please provide plausible mechanisms for the indcated transformations. Illustrate intermediates but not transition states.

**Part A, (10 points):** This reaction illustrates how diazomethane is prepared in the lab. Provide a plausible mechanism for this transformation.

**Your Mechanism**

**Part B, (10 points):** Structure **1** is called an orthoester. It may be prepared from a nitrile under the indicated reaction conditions. Provide a plausible mechanism for this transformation.

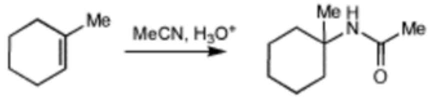
**Your Mechanism**

## Problem 601

Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz

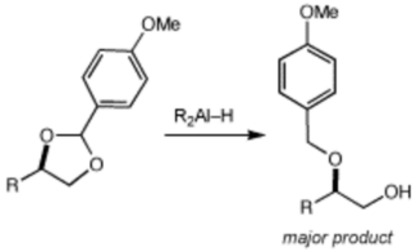
Please provide plausible mechanisms for the indcated transformations. Illustrate intermediates but not transition states.

**Part A, (10 points):** The **Ritter Reaction** formally accomplishes the addition of a nitrogen nucleophile to a double bond. Provide a plausible mechanism for this transformation.



**Your Mechanism**

**Part B, (10 points):** As you know, acetals and ketals are unreactive toward nucleophilic hydride reagents. On the other hand, Lewis acidic hydride reagents such as DIBAL will react with this functionality. One such cleavge reaction is illustrated. Provide a plausible mechanism for this transformation. Your answer must address why the more hindered benzyl ether is formed preferentially.

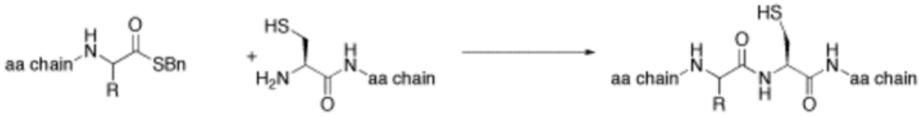


**Your Mechanism**

## Problem 606

Contributer: **Christina White**
Citation: *Science* **1994**, *266*, 776
Keywords: Mechanism quiz

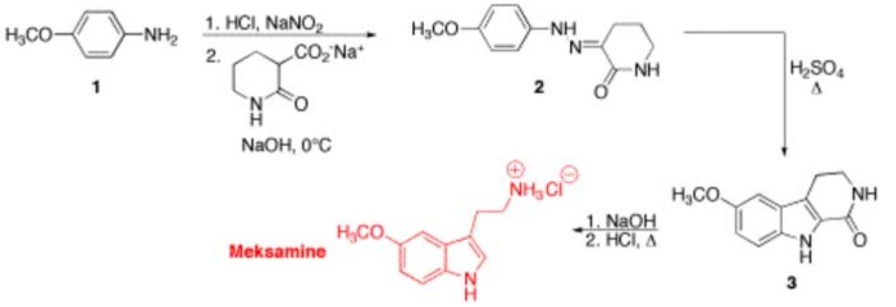
A synthetic method has been developed that allows the convergent coupling of two long peptide fragments. This method involves the coupling of one peptide with a thioester at its C-terminus and another peptide with a cysteine residue at its N-terminus. Propose a mechanism for the coupling which accounts for the fact that the cysteine residue is essential for successful coupling.



## Problem 607

Contributer: **Christina White**
Citation:
Keywords: Mechanism quiz

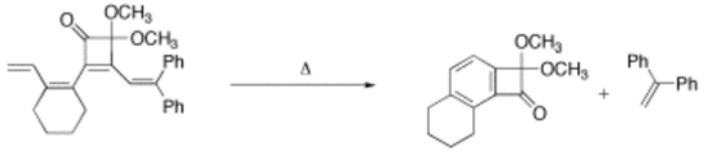
Meksamine (5-methoxytriptamine) is used for the medical treatment of radiation overdoses. The industrial synthesis of meksamine is shown below. Propose a mechanism for the formation of intermediate **2** from *p*-methoxyaniline and the formation of indole **3** from **2**. Be sure to identify any pericylic reactions that are involved in this process.



## Problem 608

Contributer: **Christina White**
Citation: *J. Org. Chem.* **1999**, *64*, 2170
Keywords: Mechanism quiz

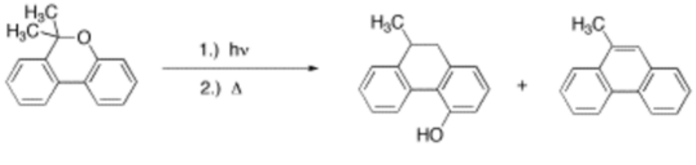
Provide a mechanism for the reaction shown below. Be sure to fully classify any pericyclic reactions.
JOC, **1999**, *64*, 2170



## Problem 609

Contributer: **Christina White**
Citation: *J. Chem Research* **1980**, 202
Keywords: Mechanism quiz

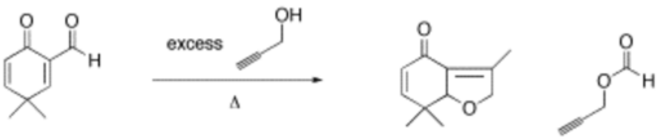
Propose a mechanism for the reaction shown. Be sure to account for both products, and fully classify any pericyclic reactions: Bowd, A.; Turnbull, J. H.; Coyle, J. D. *J. Chem. Res.* **1980**, (*S*), 202.



## Problem 612

Contributer: **Christina White**
Citation: *J. Org. Chem.* **1992**, *57*, 2467
Keywords: Mechanism quiz

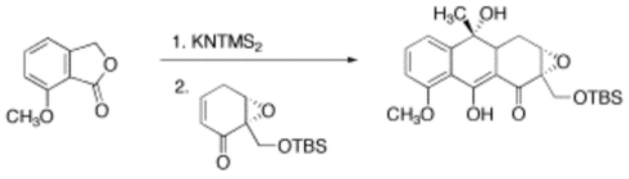
Bhat et.al. have reported the following transformation that involves an unusual pericyclic reaction as the key ring forming reaction. Please provide a mechanism for this transformation (JOC, **1992**, *57*, 2467-2468).



## Problem 616

Contributer: **Christina White**
Citation:
Keywords: Mechanism quiz

Provide a mechanism for the following transformation:

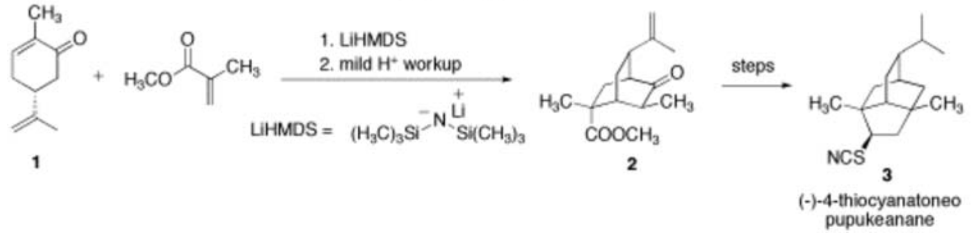


## Problem 619

Contributer: **Christina White**
Citation: *J. Org. Chem.* **2001**, *66*, 4379
Keywords: Mechanism quiz

In a recent total synthesis of (-)-4-thiocyanatoneopupukeanane (**3**), the authors assembled most of the complexity of the natural product in the first step of the synthesis to form **2**. Intermediate **2** was formed by reacting the naturally occurring chiral compound carvone (**1**) with methyl acrylate in the presence of LiHMDS, followed by acidic workup. **Provide a reasonable mechanism for the formation of (2).** Note that LiHMDS acts in the same way that LDA does.

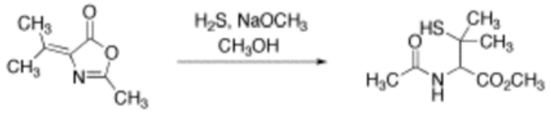
*JOC* 2001 (66) 4379


CH3
O
H3CO
CH3
1. LiHMDS
2. mild H+ workup
LiHMDS = (H3C)3Si N Li Si(CH3)3
H3C
CH3
O
COOCH3
steps
NCS
1
2
3
(-)-4-thiocyanatoneo pupukeanane

## Problem 620

Contributer: **Christina White**
Citation:
Keywords: Mechanism quiz

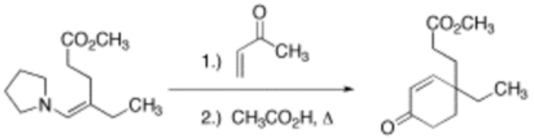
The following transformation comes from the first total synthesis of penicillin by Sheehan. Please provide a reasonable mechanism.



## Problem 621

Contributer: **Christina White**
Citation: *J. Am. Chem. Soc.* **1963**, *85*, 2872
Keywords: Mechanism quiz

Stork developed the following enamine reaction as an alternative to the Robinson annulation. Below is an example of Stork's enamine reaction (Stork, G.; Dolfini, J.E. *J. Am. Chem. Soc.* **1963**, *85*, 2872).

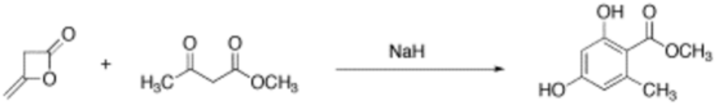


**Provide a mechanism for this reaction.**

## Problem 623

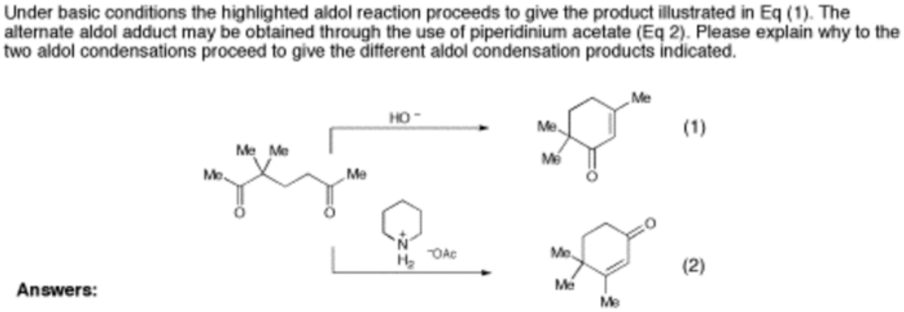
Contributer: **Christina White**
Citation: *Chem. Pharm. Bull. Japan* **1972**, *20*, 1574
Keywords: Mechanism quiz

Provide a mechanism for the following reaction (Kato, T.; Hozumi, T. *Chem. Pharm. Bull.*, **1972**, *20*, 1574).



## Problem 634

Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz



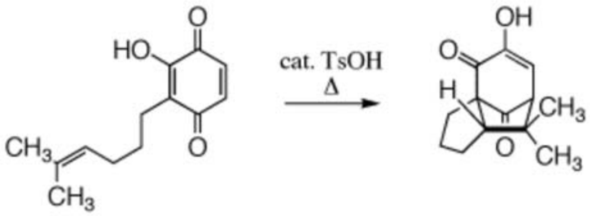
Under basic conditions the highlighted aldol reaction proceeds to give the product illustrated in Eq (1). The alternate aldol adduct may be obtained through the use of piperidinium acetate (Eq 2). Please explain why to the two aldol condensations proceed to give the different aldol condensation products indicated.

**Answers:**

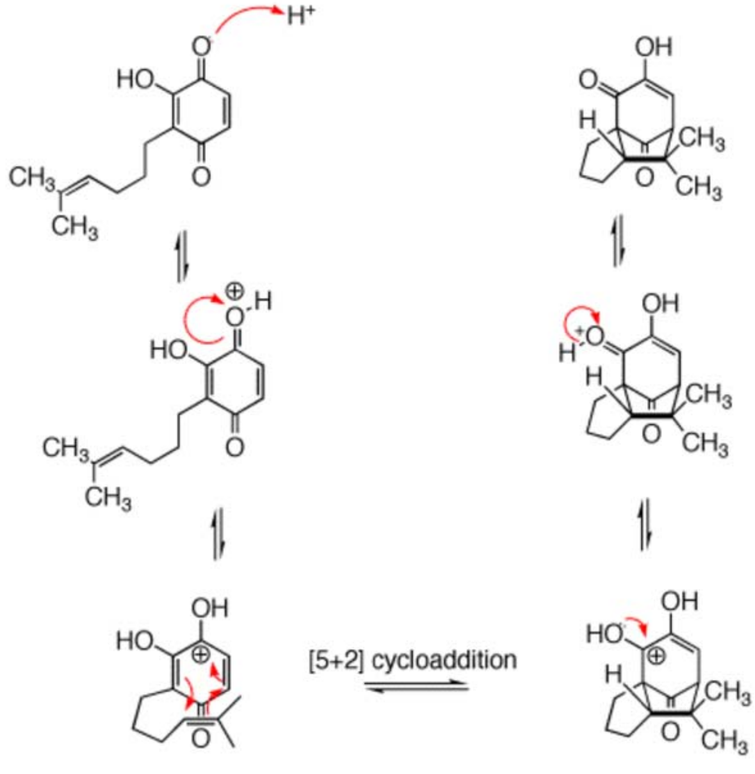
## Problem 637

Contributer: **Eric Jacobsen**
Citation:
Keywords: Mechanism quiz

Using the arrow pushing formalism, propose a reasonable mechanism for each of the transformations shown below. Be certain to classify all pericyclic reactions.

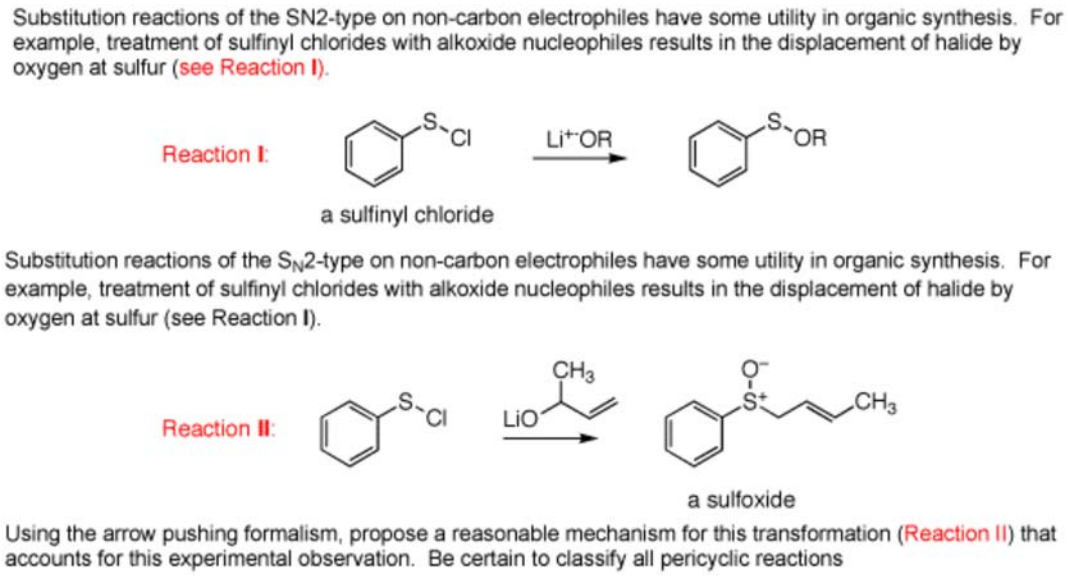


**Answer**



## Problem 638

Contributer: **David A. Evans**
Citation:
Keywords: Mechanism quiz



Substitution reactions of the SN2-type on non-carbon electrophiles have some utility in organic synthesis. For example, treatment of sulfinyl chlorides with alkoxide nucleophiles results in the displacement of halide by oxygen at sulfur (see Reaction I).

Reaction I:

S
Cl
$Li^+ {}^-OR$
S
OR

a sulfinyl chloride

Substitution reactions of the $S_N2$-type on non-carbon electrophiles have some utility in organic synthesis. For example, treatment of sulfinyl chlorides with alkoxide nucleophiles results in the displacement of halide by oxygen at sulfur (see Reaction I).

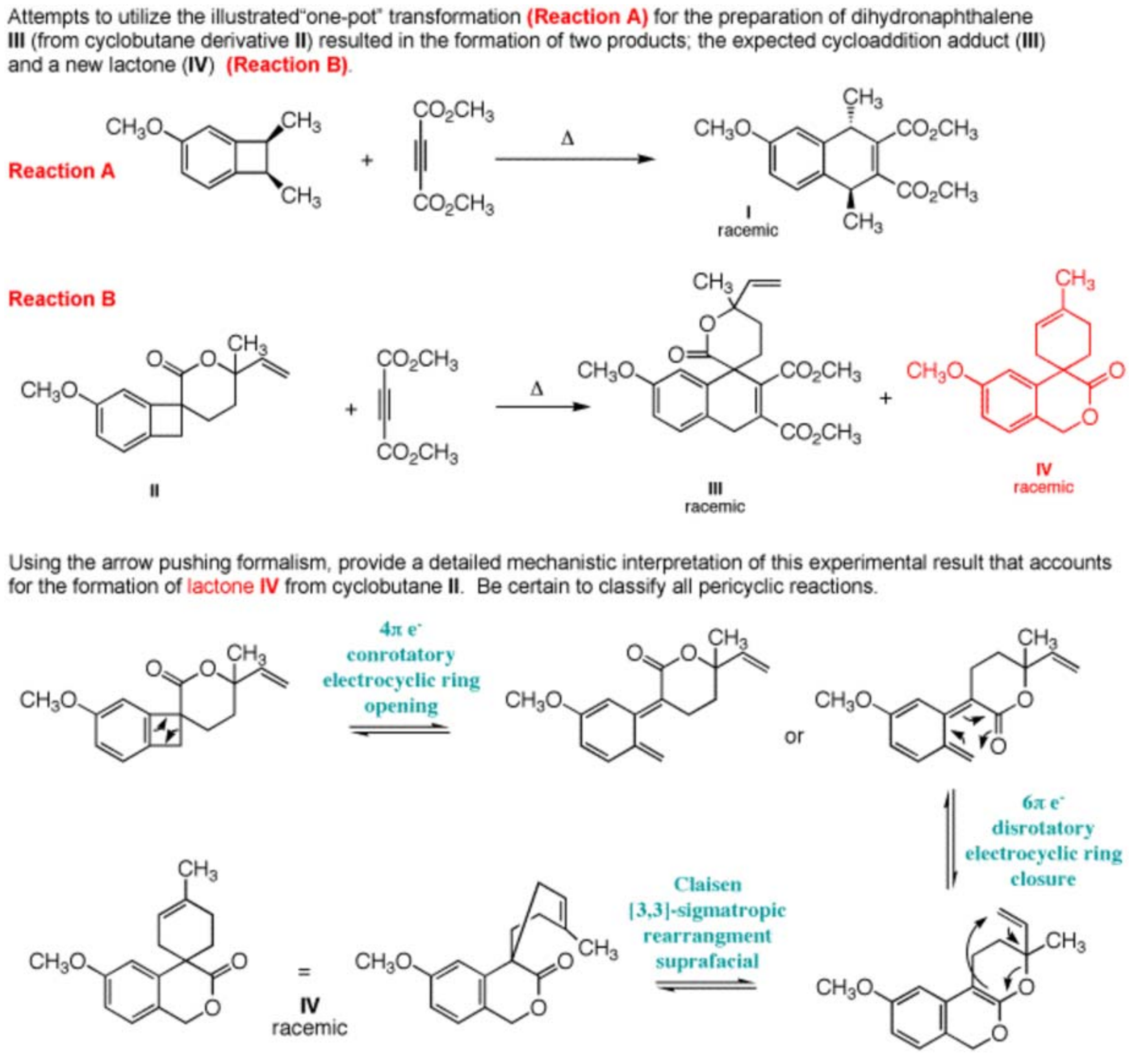
Reaction II:

a sulfoxide

Using the arrow pushing formalism, propose a reasonable mechanism for this transformation (Reaction II) that accounts for this experimental observation. Be certain to classify all pericyclic reactions

## Problem 641

Contributer: **Eric Jacobsen**
Citation:
Keywords: Mechanism quiz



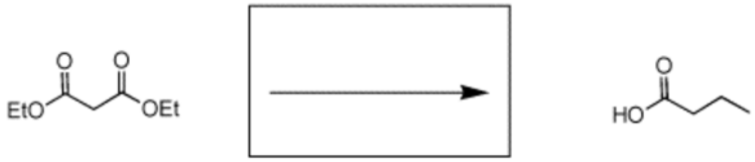
Attempts to utilize the illustrated"one-pot" transformation **(Reaction A)** for the preparation of dihydronaphthalene **III** (from cyclobutane derivative **II**) resulted in the formation of two products; the expected cycloaddition adduct (**III**) and a new lactone (**IV**) **(Reaction B)**.

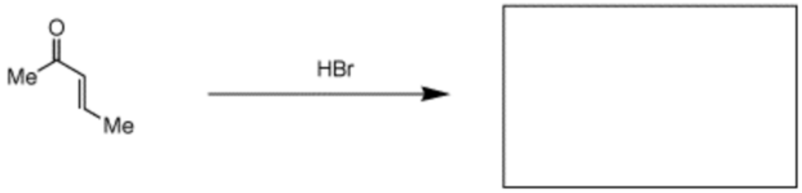
Using the arrow pushing formalism, provide a detailed mechanistic interpretation of this experimental result that accounts for the formation of lactone **IV** from cyclobutane **II**. Be certain to classify all pericyclic reactions.

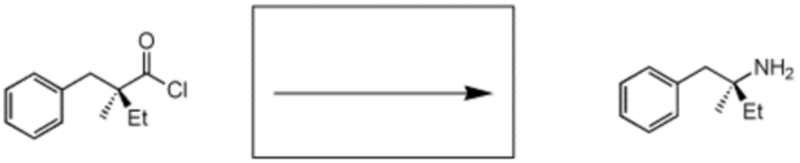
**Problem 647**

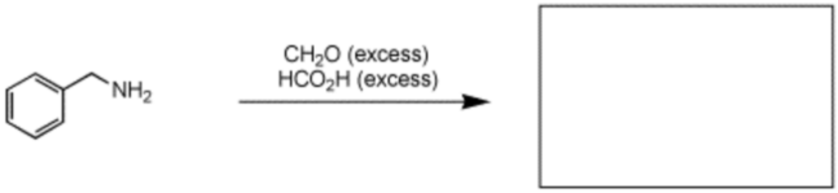
Contributer: **Eric Jacobsen**
Citation:
Keywords: Reaction quiz

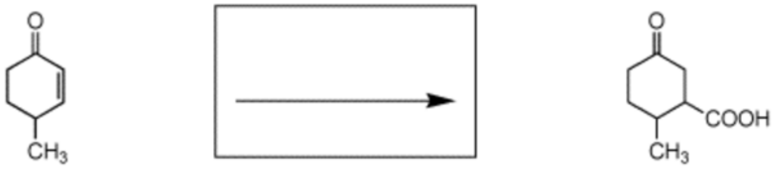
Predict the product or provide reagents to accomplish each of the following transformations. More than 1 step may be required to complete a transformation.









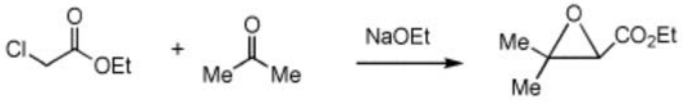


## Problem 649

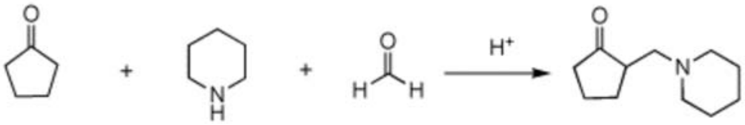
Contributer: **Eric Jacobsen**
Citation:
Keywords: Mechanism quiz

"Famous Names" The aldol reaction is a fundamental reaction in organic chemistry for which numerous derivatives exist, each bearing the name of its discoverer. Although the reagents may differ, the mechanisms remain similar. Using the curved-arrow formalism, provide a mechanism for each of the following analogs of the aldol reaction.

**Darzen:**



**Mannich:**

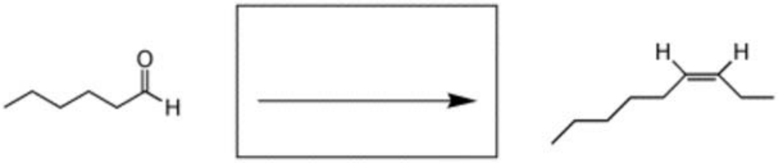


## Problem 652

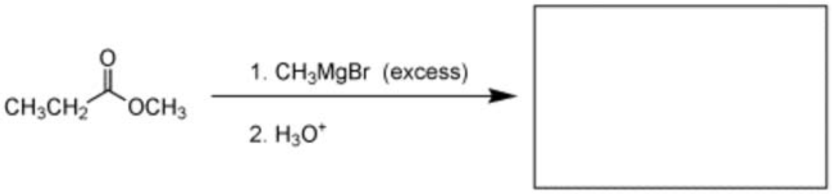
Contributer: **Eric Jacobsen**
Citation:
Keywords: Reaction quiz

Predict the major product or provide reagents to accomplish each of the following transformations. More than 1 step may be required to complete a transformation.

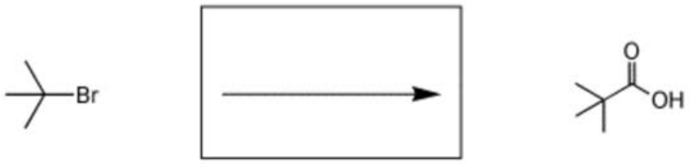
**Part A:**



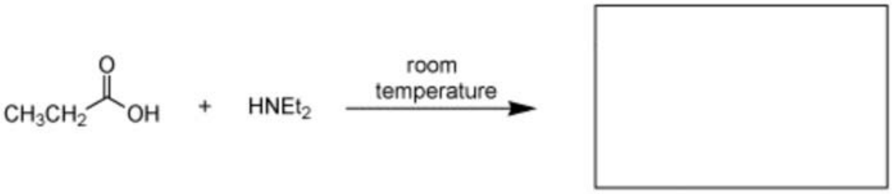
**Part B:**



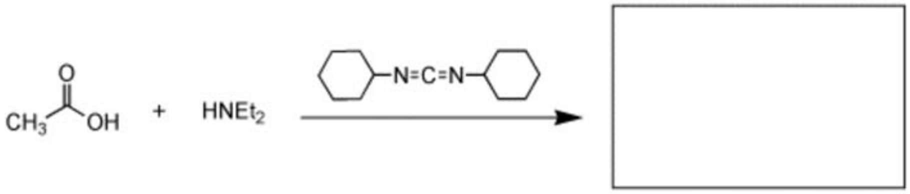
**Part C:**



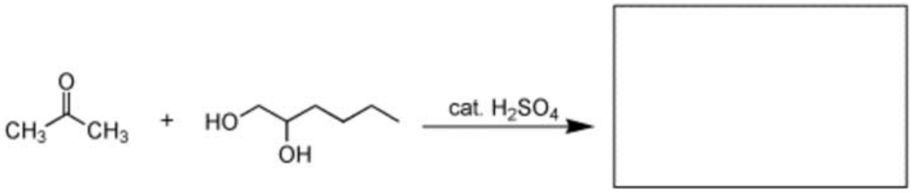
**Part D:**



**Part E:**

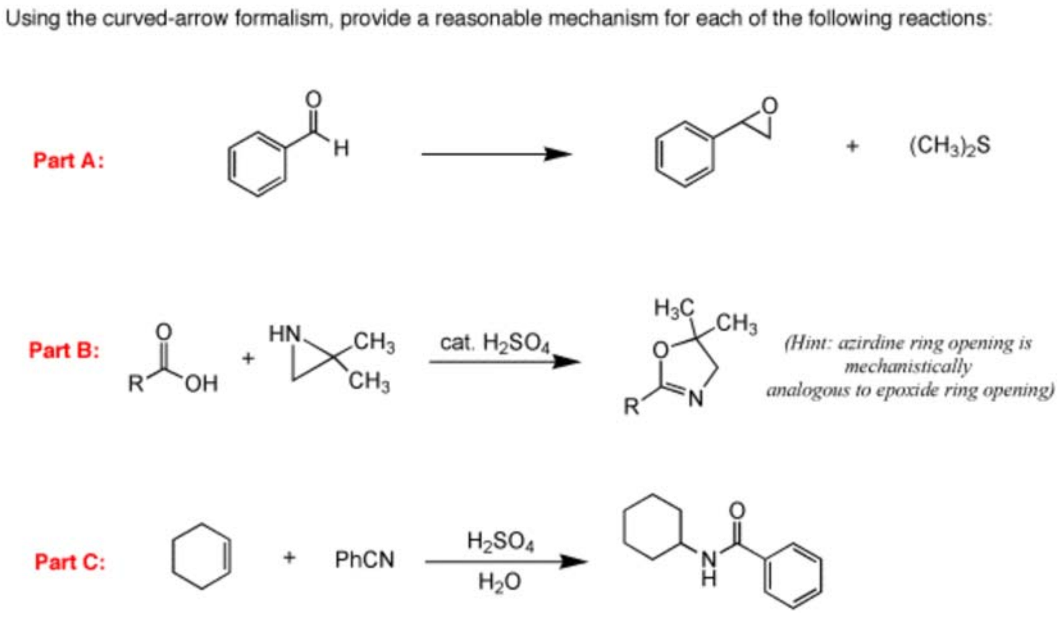


**Part F:**



## Problem 660

Contributer: **Eric Jacobsen**
Citation:
Keywords: Mechanism quiz



Using the curved-arrow formalism, provide a reasonable mechanism for each of the following reactions:

**Part A:**

**Part B:**

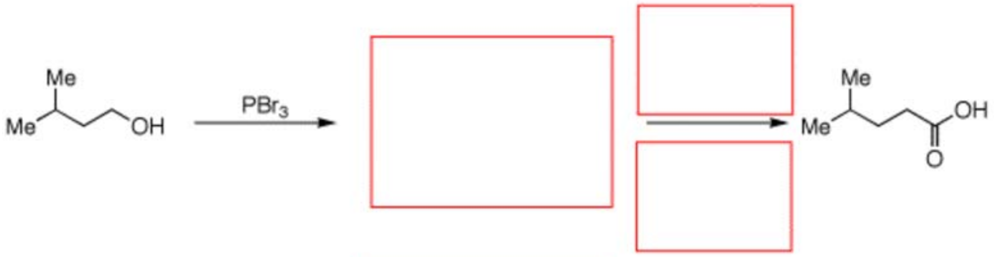
*(Hint: azirdine ring opening is mechanistically analogous to epoxide ring opening)*

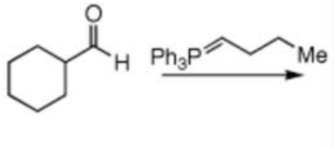
**Part C:**

## Problem 661

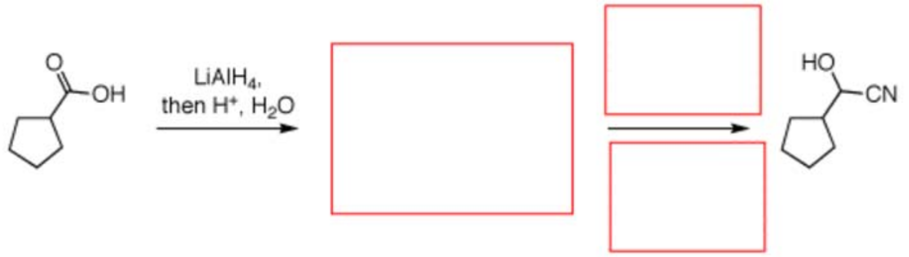
Contributer: **Eric Jacobsen**
Citation:
Keywords: Reaction quiz

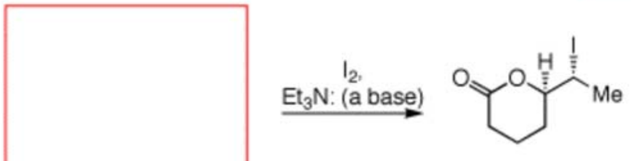
Predict the major product or provide all reagents to accomplish each of the following transformations.
(NOTE: More than one (1) step may be required to complete each transformation)





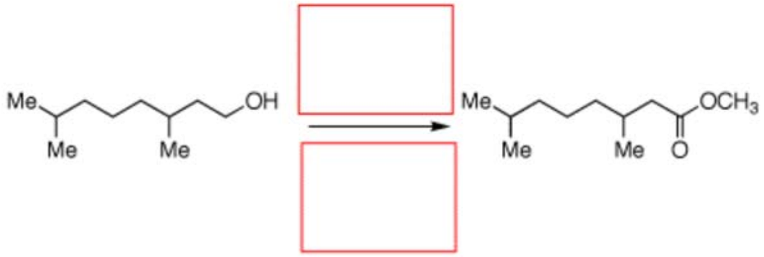
(show relevant stereochemistry)





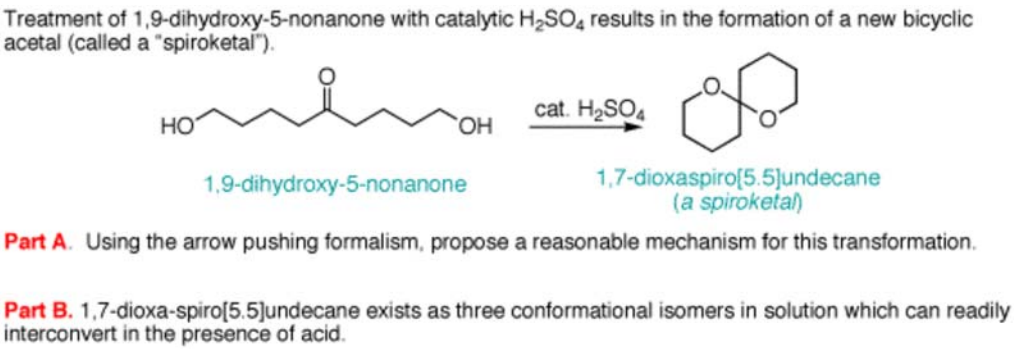
(show relevant stereochemistry)

racemic



## Problem 663

Contributer: **Eric Jacobsen**
Citation:
Keywords: Mechanism quiz



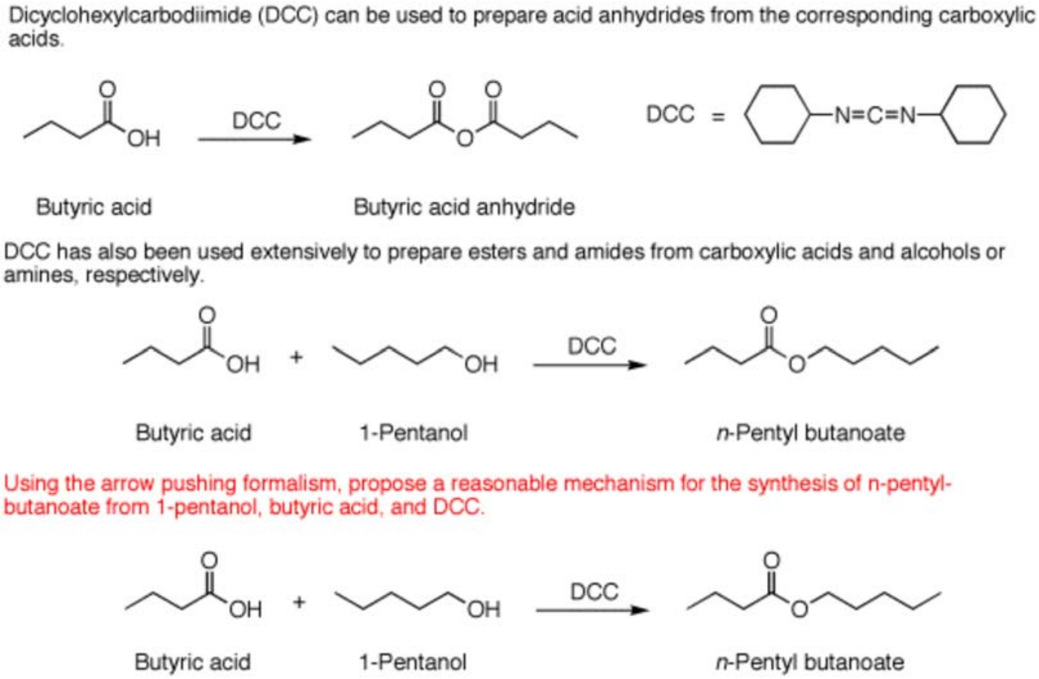
Treatment of 1,9-dihydroxy-5-nonanone with catalytic $H_2SO_4$ results in the formation of a new bicyclic acetal (called a "spiroketal").

**Part A**. Using the arrow pushing formalism, propose a reasonable mechanism for this transformation.

**Part B.** 1,7-dioxa-spiro[5.5]undecane exists as three conformational isomers in solution which can readily interconvert in the presence of acid.

## Problem 664

Contributer: **Eric Jacobsen**
Citation:
Keywords: Mechanism quiz



Dicyclohexylcarbodiimide (DCC) can be used to prepare acid anhydrides from the corresponding carboxylic acids.

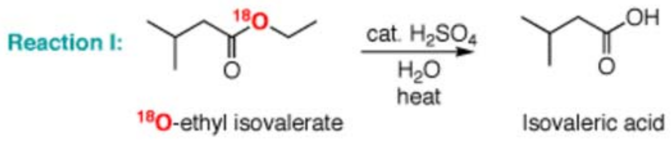
DCC has also been used extensively to prepare esters and amides from carboxylic acids and alcohols or amines, respectively.

Using the arrow pushing formalism, propose a reasonable mechanism for the synthesis of n-pentyl-butanoate from 1-pentanol, butyric acid, and DCC.

## Problem 665

Contributer: **Eric Jacobsen**
Citation:
Keywords: Mechanism quiz

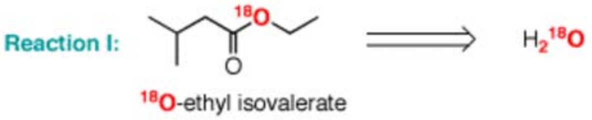
In a study of the mechanism of acid-catalyzed hydrolysis of primary, unbranched alkyl esters, isotopically labeled ethyl isovalerate ($^{18}$O-ethyl isovalerate) was synthesized.



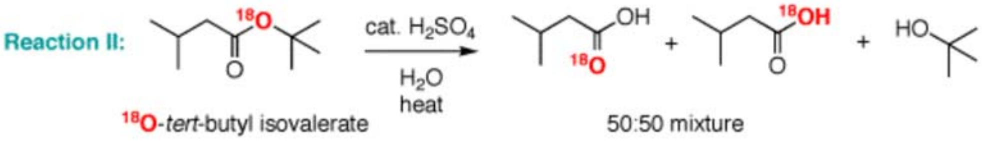
Treatment of $^{18}$O-ethyl isovalerate with aqueous acid (cat. $H_2SO_4$, $H_2O$) results in the quantitative formation of isovaleric acid.

**Part A.** Using the arrow pushing formalism, propose a reasonable mechanism for this transformation that is consistent with the observation that isovaleric acid (the product of the hydrolysis reaction) has no isotopic enrichment at either oxygen of the carboxylic acid **(Reaction I).**

**Part B.** Starting with $H_2{}^{18}O$ as your only source of isotopically enriched oxygen, propose a synthesis of $^{18}$O-ethyl isovalerate. You may use any additional compounds and/or reagents your synthetic route may require.



**Part C.** Surprisingly, the hydrolysis of the isotopically labeled tert-butyl ester of isovaleric acid ($^{18}$O-tert-butyl isovalerate) results in the formation of a carboxylic acid that retains the isotopic label **(Reaction II).**

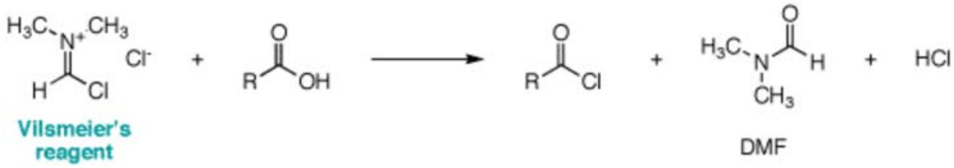


Using the arrow pushing formalism, propose a reasonable mechanism for the production of all three (3) new compounds that is consistent with this observation.

## Problem 667

Contributer: **Eric Jacobsen**
Citation:
Keywords: Mechanism quiz

Treatment of a carboxylic acid with Vilsmeier's reagent results in the formation of an acid chloride.

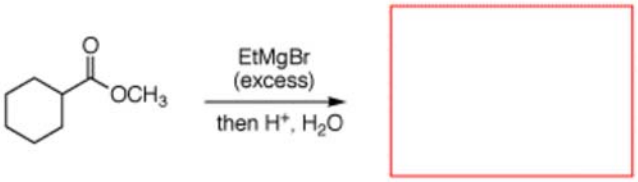


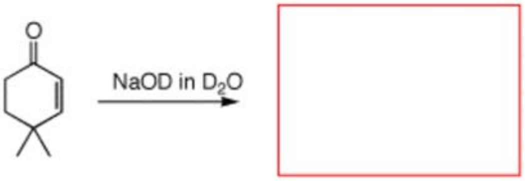
Using the arrow pushing formalism, propose a reasonable mechanism for this transformation.

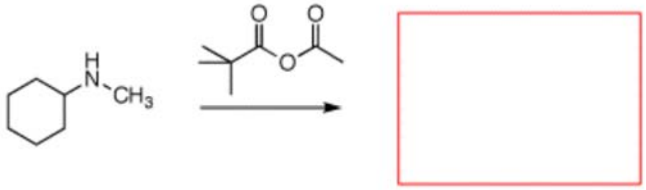
## Problem 668

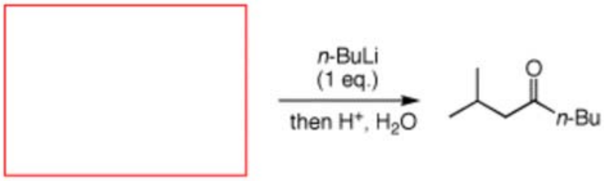
Contributer: **Eric Jacobsen**
Citation:
Keywords: Reaction quiz

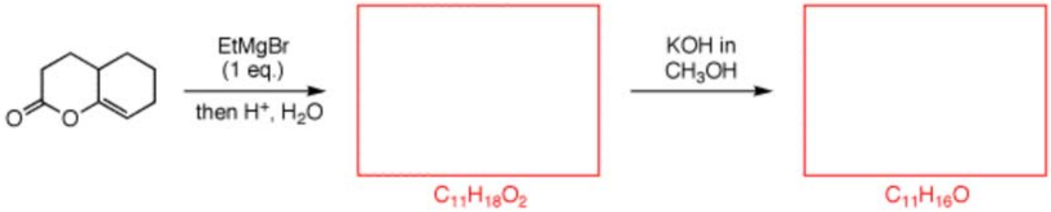
Predict the major product or provide the starting materials necessary to accomplish each of the following transformations.







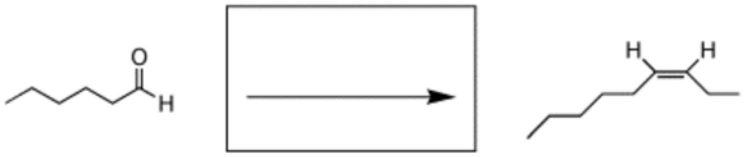


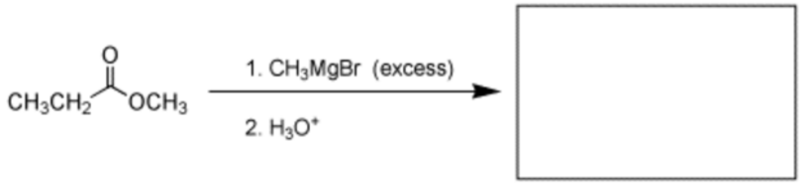


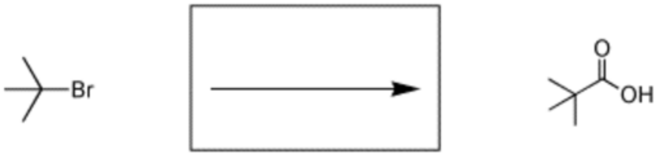
**Problem 679**

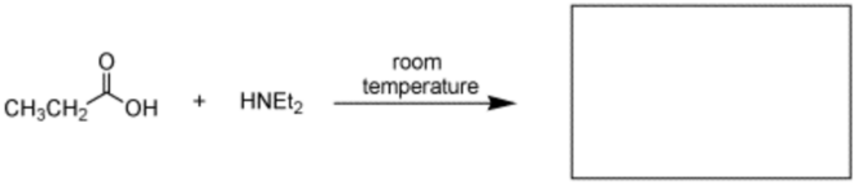
Contributer: **Eric Jacobsen**
Citation:
Keywords: Reaction quiz

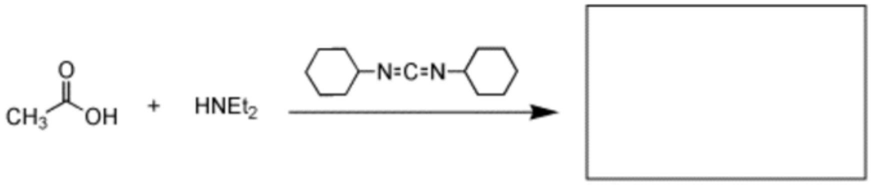
Predict the major product or provide reagents to accomplish each of the following transformations. More than 1 step may be required to complete a transformation.

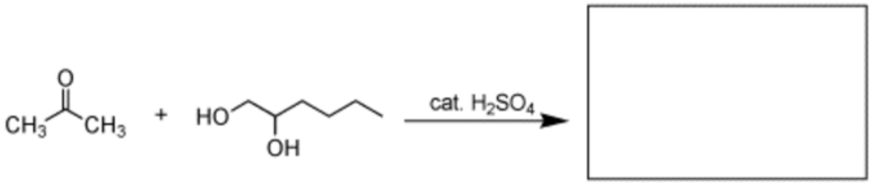








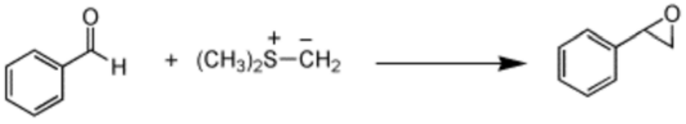




## Problem 685

| | |
|---|---|
| Contributer: | **Eric Jacobsen** |
| Citation: | |
| Keywords: | Mechanism quiz |

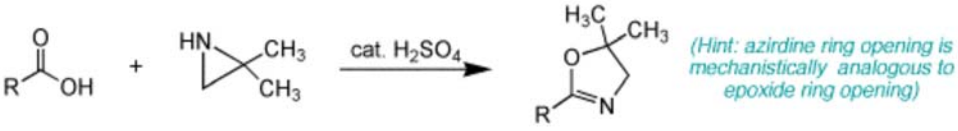
Using the curved-arrow formalism, provide a reasonable mechanism for each of the following reaction:



## Problem 686

Contributer: **Eric Jacobsen**
Citation:
Keywords: Mechanism quiz

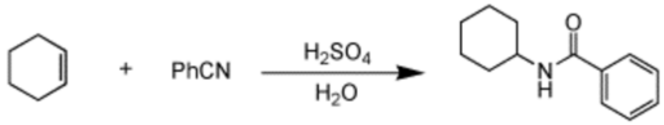
Using the curved-arrow formalism, provide a reasonable mechanism for each of the following reactions:


cat. $H_2SO_4$
(Hint: azirdine ring opening is mechanistically analogous to epoxide ring opening)

## Problem 687

Contributer: **Eric Jacobsen**
Citation:
Keywords: Mechanism quiz

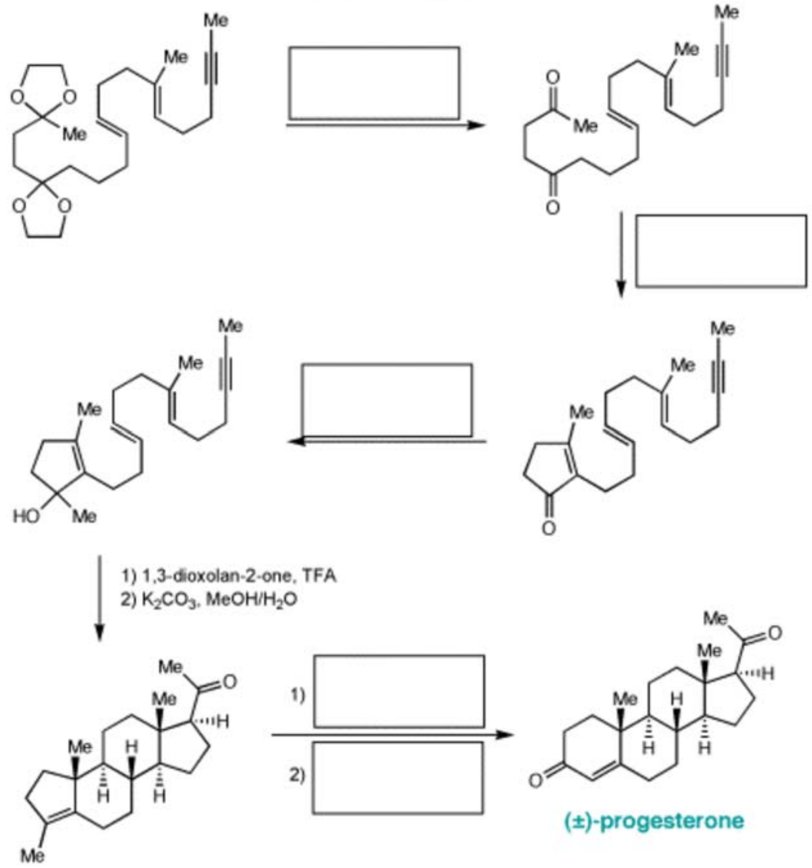
Using the curved-arrow formalism, provide a reasonable mechanism for each of the following reaction:



## Problem 692

Contributer: **Jimmy Wu**
Citation:
Keywords: Reaction quiz

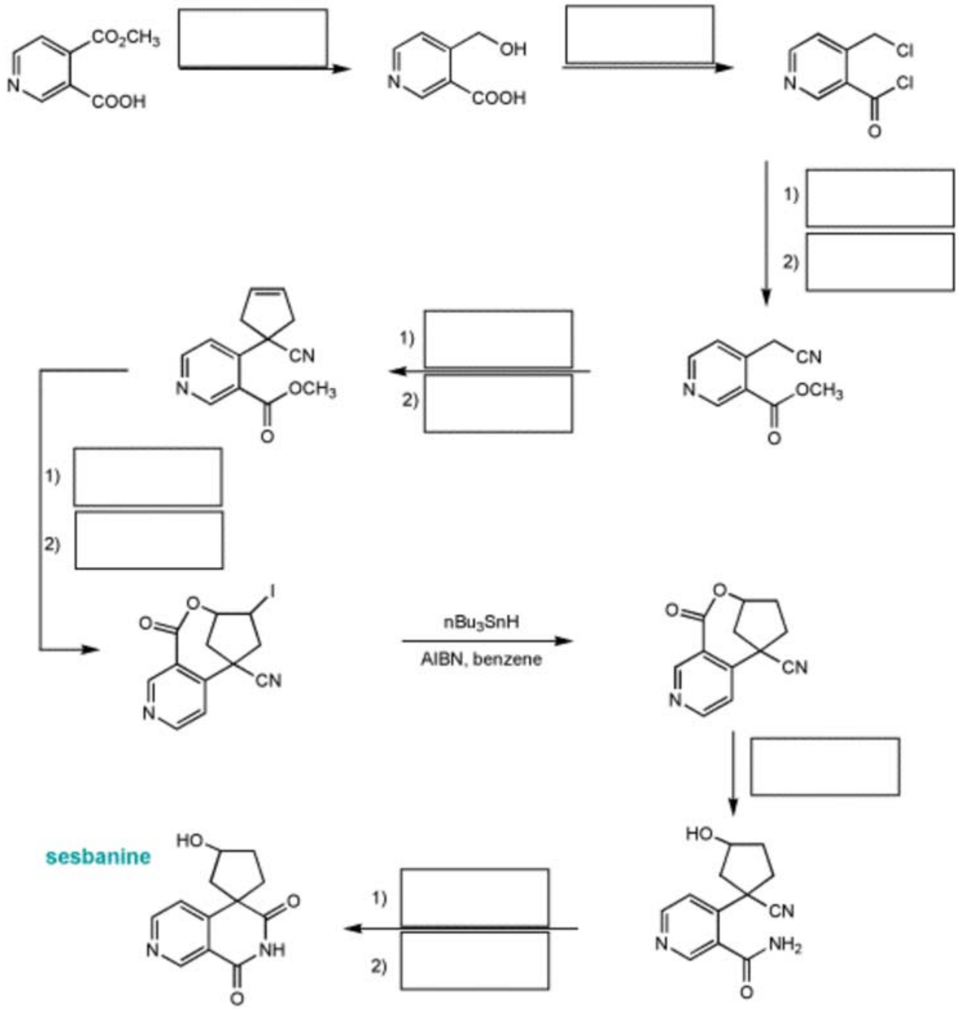
Please fill in the missing reagents in the following synthesis of progesterone.



## Problem 693

Contributer: **Paul Bracher**
Citation: *J. Org. Chem.* **1980**, *45*, 1176
Keywords: Reaction quiz

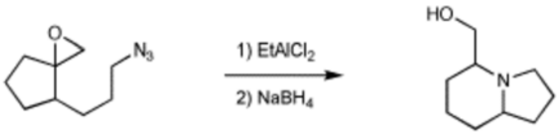
Please fill in the missing reagents in the following synthesis of sesbanine reported by Berchtold. (*J. Org. Chem.* **1980**, *45*, 1176.)



## Problem 695

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2003**, *55*, 583-585
Keywords: Mechanism quiz

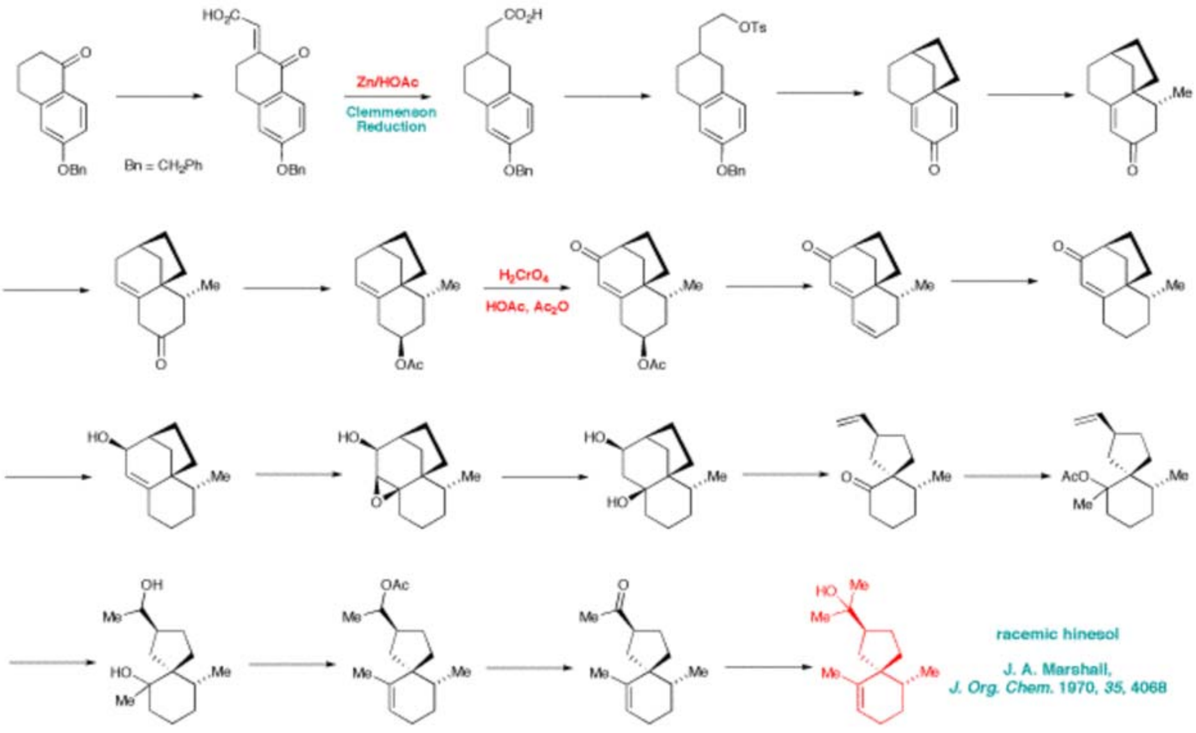
Propose a mechanism for the following transformation reported by Reddy and co-workers (*Org. Lett.* **2003**, *5*, 583-585).



## Problem 752

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1970**, *35*, 4068
Keywords: Reaction quiz

In 1970, Marshall and Brady completed the first synthesis of the sesquiterpene hinesol by the route outlined below (*J. Org. Chem.* **1970,** *35*, 4068). Using your knowledge of organic chemistry, fill in the appropriate reagents and other building blocks that would be needed to complete this synthesis. You do not need to record normal acid or base isolations.



**Answers**

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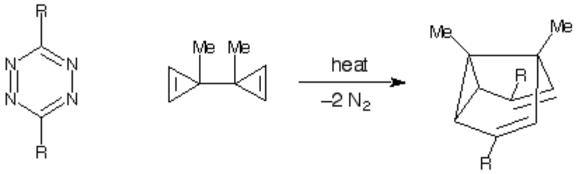
## Advanced Organic Chemistry Cumulative Exams, Chem 206

### Problem 1

Contributer: **David A. Evans**
Citation: *Eur, J. Chem.* **2002**, 791-801
Keywords: Rearrangement

The following "one-pot" synthesis of semibulvalene was recently reported by J. Sauer (*Eur. J. Chem.* **2002**, 791-801).

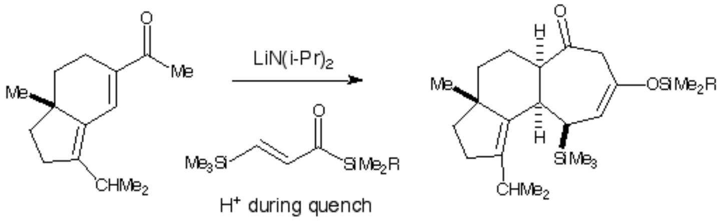


Provide a plausible mechanism for this transformation in the space below:

### Problem 10

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2000**, *2*, 1903
Keywords: Rearrangement

Takeda and co-workers have recently reported the mechanistically interesting ring extension reaction illustrated below (*Org. Lett.* **2000**, 2, 1903).

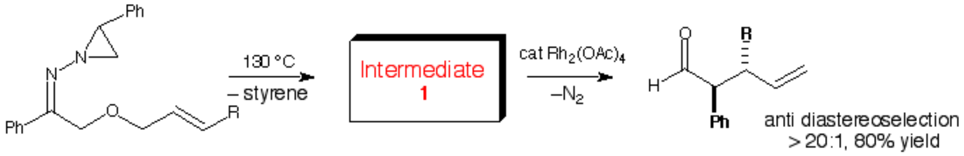


Provide a plausible mechanism for this transformation in the space below.
*Ignore the stereochemical aspect of this transformation.*

### Problem 13

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2002**, *124*, 12426
Keywords: Rearrangement

The following transformation was recently reported by Stoltz (*J. Am. Chem. Soc* **2002**, *124*, 12426). In addition to the illustrated product, styrene and dinitrogen are produced as by-products in this transformation.

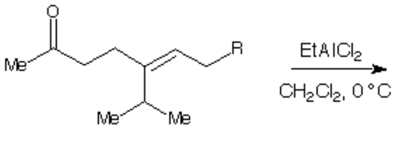


Provide a plausible mechanism for this transformation in the space below and identify intermediate **1**. Your mechanism should provide a rationalization for the product stereochemical relationship.

### Problem 17

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2001**, *3*, 569-572
Keywords: Rearrangement

The reaction illustrated below was recently reported by Snider and co-workers (Org. Lett. **2001**, *123*, 569-572). Provide a mechanism for this transformation in the space below. Where stereochemical issues are present, provide clear three dimensional drawings to support your answer.

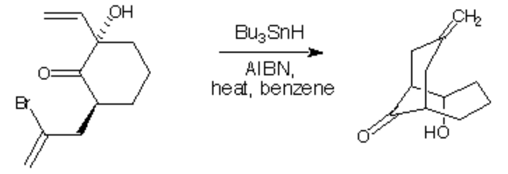


## Problem 18

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2001**, *3*, 1181-1183
Keywords: Rearrangement

The following transformation was recently reported by Rodriguez (*Org. Lett.* **2001**, *3*, 1181-1183).

**A**



**B**

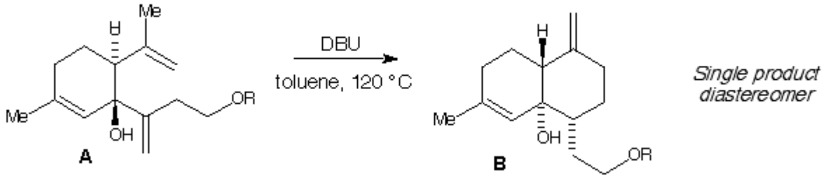
**Part A** What is the structure and function of AIBN in this reaction?

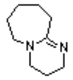
**Part B** Provide a mechanism for the illustrated rearrangement(s) of **A** to **B**. Where stereochemical issues are present, provide clear three dimensional drawings to support your answer.

## Problem 19

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2001**, *3*, 1925-1927
Keywords: Rearrangement

The following transformation was recently reported by Barriault and Deon in conjunction with their synthesis of arteanniun M (*Org. Lett.* **2001**, *3*, 1925-1927). Provide a mechanism for the illustrated thermal rearrangement(s) of **A** to **B**. Where stereochemical issues are at stake, provide clear three dimensional drawings to support your answer.





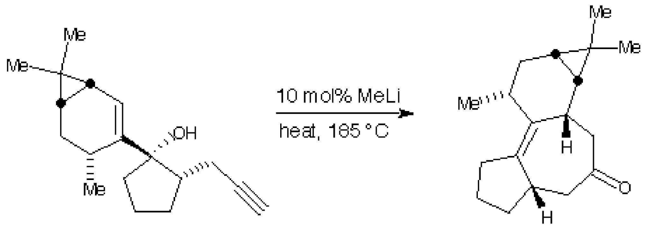
DBU is a useful amidine base; pKa ~ 12

Provide your answer in the space below:

## Problem 20

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2001**, *3*, 115-117
Keywords: Rearrangement

T. V. Ovaska and co-workers have recently reported the complex rearrangement illustrated below as an entry into the phorbol skeleton (*Org. Lett* **2001**, *3*, 115-117). Provide a mechanism for the illustrated transformation. Where stereochemical features are an issue, provide clear three dimensional drawings to support your answer.

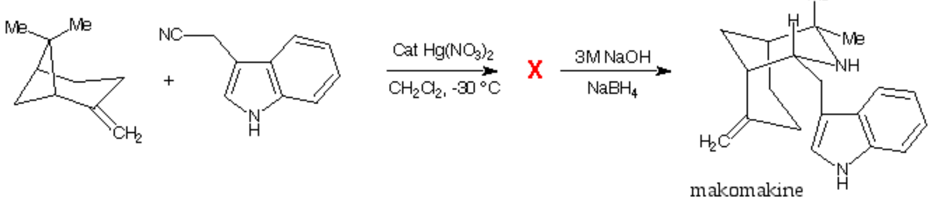


Provide your answer in the space below:

## Problem 22

Contributer: **David A. Evans**
Citation: *Chem. Commun.* **1983**, 384
Keywords: Rearrangement

An interesting example of the **Ritter Reaction** was reported some time ago by R. V. Stevens (*Chem. Comm.* 384 **1983**). The relevant process illustrated below afforded an efficient two-step synthesis of makomakine. In contemplating this transformation, view Hg(2+), to be functioning as a catalyst in the production of **X**.

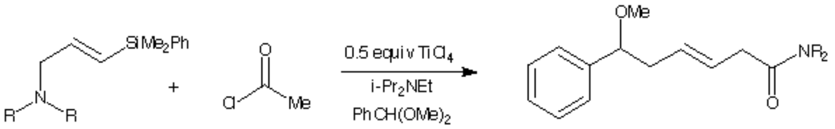


In the space below, provide a mechanism for the illustrated two-step transformation and identify the structure **X**.

## Problem 31

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1999**, *121*, 9726
Keywords: Rearrangement

In the Panek lecture he described the transformation illustrated below. This transformation is an extrapolation of the recent publication of MacMillan and co-workers (*JACS*, **1999**, *121*, 9726).

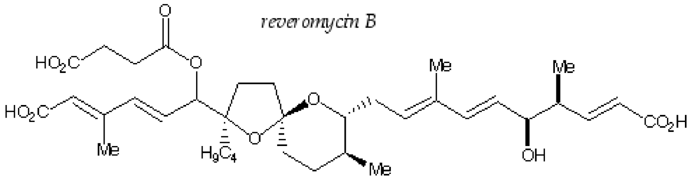


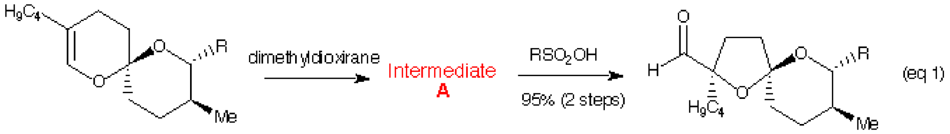
Provide a detailed mechanism for the illustrated transformation. Use three-dimensional representations, where relevant, to illustrate the stereochemical aspects of the individual steps.

## Problem 33

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2000**, *2*, 191
Keywords: Rearrangement

Recently, Rizacassa reported the synthesis of the spiroketal-containing natural product reveromycin B. An important transformation in this synthesis was the rearrangement illustrated below (eq 1) (Rizacassa *Org. Letters.* **2000**, 2, 191).





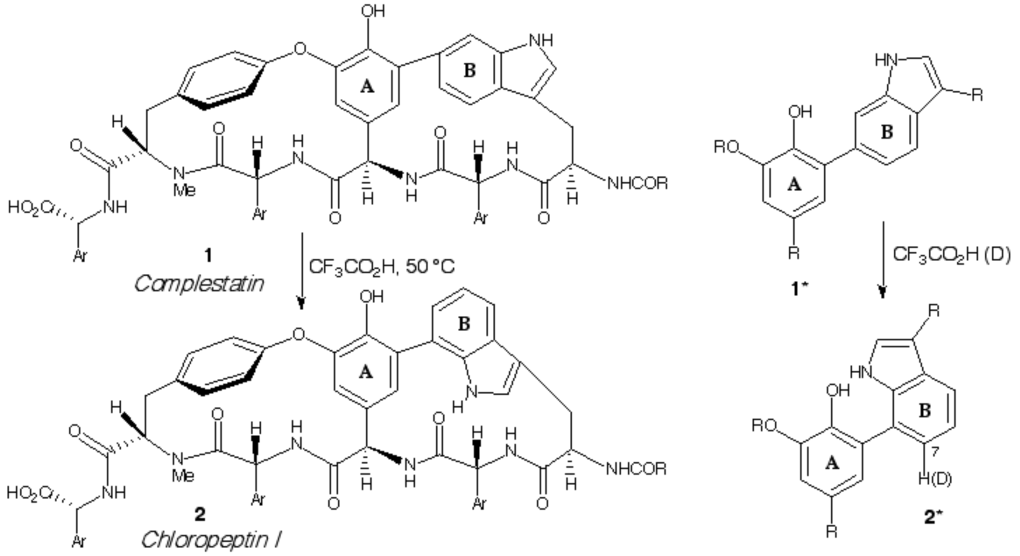
(eq 1)

Provide a mechanism for the overall transformation in the space below. It is important that you deduce the stereochemistry of intermediate **A**. Use three-dimensional representations, where relevant, to illustrate the stereochemical aspects of the individual steps.

## Problem 36

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1998**, *39*, 2247-2248
Keywords: Rearrangement

Patane and co-workers recently documented the unusual acid-induced rearrangement of complestatin (**1**) to the related natural product chloropeptin I (**2**) (*Tetrahedron Lett.* **1998**, *39*, 2247-2248). This observation is significant since it raises the prospect that the two natural products might be biogenetically related through the illustrated rearrangement.



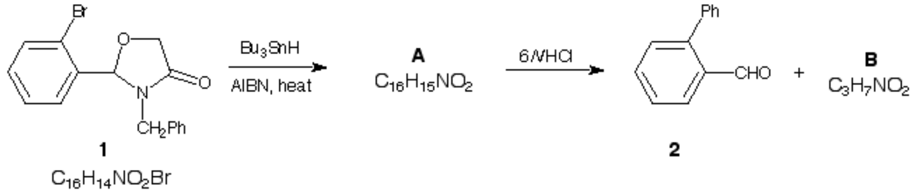
**Part A.** In the space below, draw out each of the intermediates that might be anticipated in the transformation of **1** to **2**. For simplicity use the structures **1*** and **2*** in answering this question. Your mechanism should accommodate the specific D(+) incorporation at position 7 of the indole nucleus.

**Part B.** In your opinion, what is providing the driving force for this rearrangement.

## Problem 38

Contributer: **David A. Evans**
Citation: *Helv. Chem. Acta* **1997**, *80*, 2148-2156
Keywords: Rearrangement

The transformation illustrated below was recently reported by Giraud (*Helv. Chim. Acta* **1997**, *80*, 2148-56).

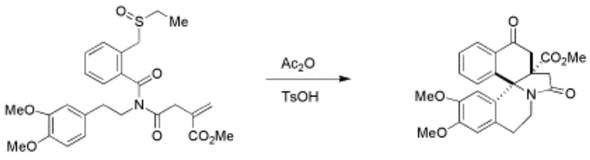


In the space below, draw out each of the intermediates that might be anticipated in the transformation of **1** to the illustrated products. Please provide the structures for **A**, and **B**.

## Problem 41

Contributer: **Robert M. Williams**
Citation: *Tetrahedron Lett.* **1995**, *36*, 3495-3498
Keywords: Rearrangement

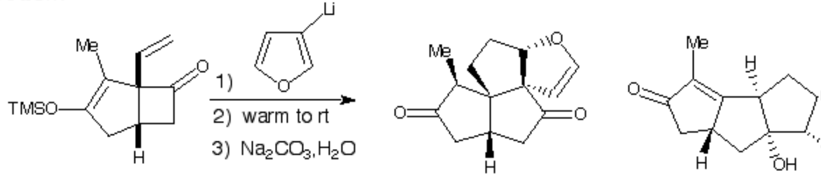
Padwa reported the interesting transformation shown below. Provide a detailed mechanism and identify any organic named reactions in this sequence. (Padwa, A. *Tet. Lett.*, **1995**, *36*(20), 3495-3498)



## Problem 43

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1996**, *61*, 7976
Keywords: Rearrangement

Moore (*J. Org. Chem.* **1996**, *61*, 7976) recently reported the elegant 3-step transformation that is illustrated by the specific example below.



**1**, major (57%) **2**, minor (11%)

**Part A.** Draw out a plausible mechanism for the transformation to the major product isomer **1**.

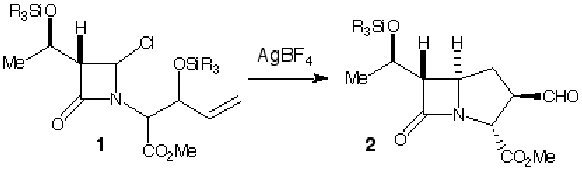
**Part B.** Draw out a plausible mechanism for the transformation to the minor product isomer **2**.

## Problem 46

Contributer: **David A. Evans**
Citation: *Chem. Commun.* **1995**, 2527
Keywords: Rearrangement

Sakurai (*Chem. Commun.* **1995**, 2527) recently reported the silver ion induced rearrangement of **1** to the bicyclic β-lactam **2**.

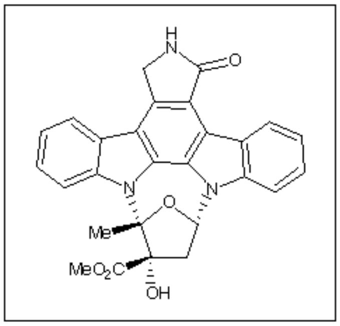
Provide a plausible mechanism for this transformation in the space below.

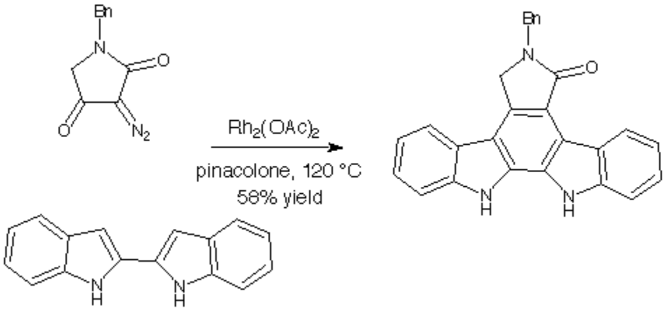


## Problem 47

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1995**, *117*, 10413
Keywords: Rearrangement

Wood recently reported a very clever approach to the synthesis of the indolocarbazole family of natural products (*JACS* **1995**, *117*, 10413). His approach to the indolocarbazole core is the one-pot transformation outlined below.



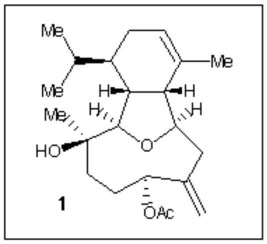


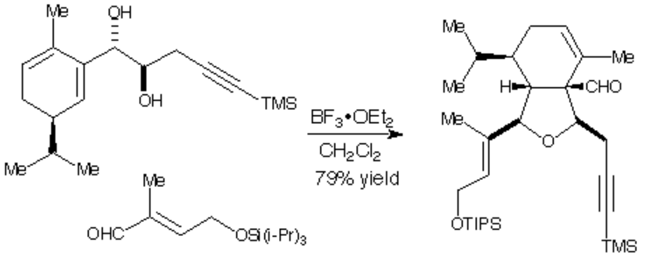
Provide a plausible mechanism for this multi-step transformation in the space below.

## Problem 49

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1995**, *117*, 10391
Keywords: Rearrangement

Overman and MacMillan (*JACS* **1995**, *117*, 10391) recently reported the synthesis of the diterpene, 7-deacetoxyalcyonin (**1**) illustrated below. The keynote reaction in this synthesis is the Lewis acid catalyzed transformation illustrated below, a process that has previously been investigated in the Overman Group (*JACS* **1991**, *113*, 3534).



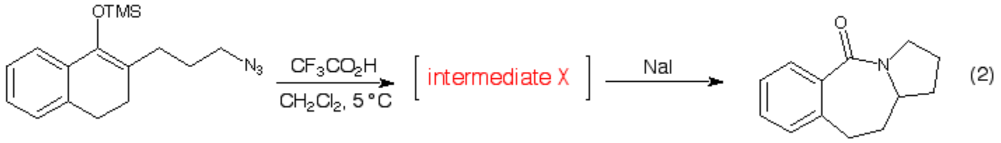


Propose a detailed mechanism for this transformation. Be sure to clearly identify the stereochemical control elements that are operating in the creation of the new stereogenic centers.

## Problem 51

Contributer: **David A. Evans**
Citation: *Tetrahedron* **1996**, *52*, 3403
Keywords: Rearrangement

Aube (*Tetrahedron* **1996**, 52, 3403) recently reported an efficient approach to the synthesis of polycyclic lactams. A typical transformation is provided below (eq 2).

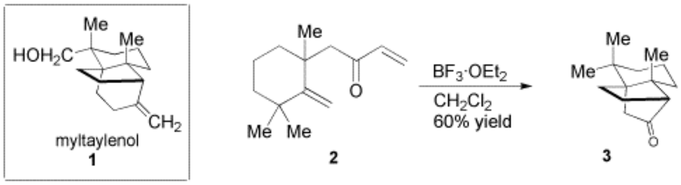


Provide a plausible mechanism for this transformation in the space below.

## Problem 56

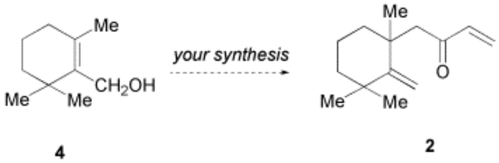
Contributer: **Grace Wang**
Citation: *Chem. Commun.* **1994**, 2259
Keywords: Rearrangement

The recently isolated irregular sesquiterpene myltaylenol (**1**) stimulated Srikrishna and co-workers (*Chem. Commun.* **1994**, 2259) to study the biogenetically modeled acid-promoted rearrangement of **2** which leads to the desired terpenoid skeleton in good yield. In the space below, provide a detailed mechanism for the transformation of **2** to **3**.



A.Srikrishna, *Chem. Commun.* **1994**, 2259.

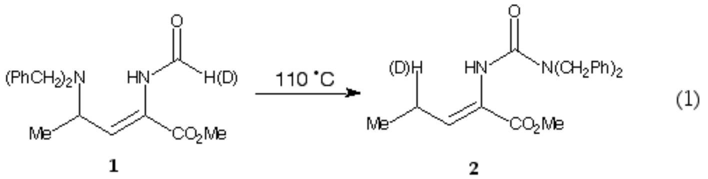
Provide an expedient synthesis of **2** from the allylic alcohol **4**.



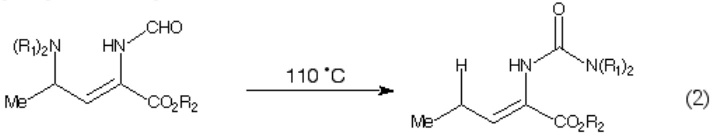
## Problem 57

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1993**, *34*, 579
Keywords: Rearrangement

Kende recently reported (*Tetrahedron Lett.* **1993, 34,** 579) the intriguing thermal rearrangement shown below (eq 1). In this rearrangement the H & $NR_2$ are effectively interchanged. When the formyl H is replaced with D, the deuterium label also transfers.



To provide information on the mechanism of the reaction, a cross-over experiment was carried out (eq 2). In this experiment, equal quantities of **1** and **3** , carrying different ester and amine moieties, were combined and rearranged to afford equal quantities of products **4a-4d.**



**1,** $R_1 = N(CH_2Ph)_2$, $R_2 = Me$

**3,** $R_1 = N(CH_2PhCl)_2$, $R_2 = Et$

**4a,** $R_1 = N(CH_2Ph)_2$, $R_2 = Me$

**4b,** $R_1 = N(CH_2PhCl)_2$, $R_2 = Et$

**4c,** $R_1 = N(CH_2PhCl)_2$, $R_2 = Me$

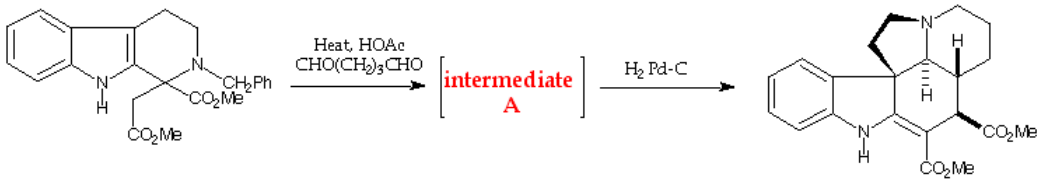
**4d,** $R_1 = N(CH_2Ph)_2$, $R_2 = Et$

Provide a mechanism for this reaction that is consistent with the information provided. An additional bit of information on this transformation was provided with a continuous IR scan of the reaction which reveals the buildup of a sharp absorbance in the region at 2220 cm-1 which disappears upon formation of product. Identify the intermediate that is responsible for this IR band.

## Problem 60

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1987**, *28*, 1267
Keywords: Rearrangement

Provide a detailed mechanism for the cyclization reported by Vercautern and co-workers (*Tetrahedron Lett.* **1987,** *28*, 1267).

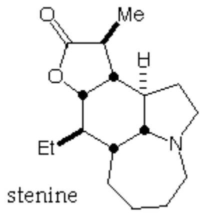


**Your mechanism for this transformation**

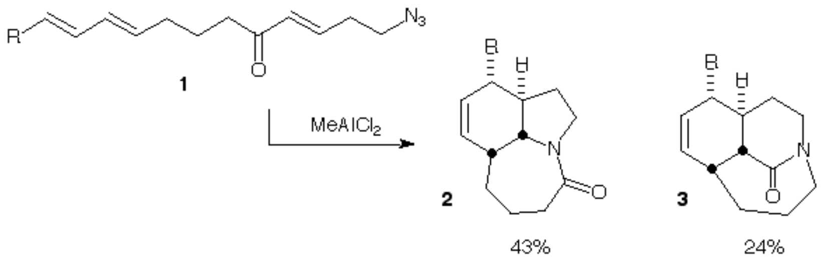
## Problem 72

Contributer: **David A. Evans**
Citation: *Angew. Chem.* **2002**, *41*, 4316
Keywords: Rearrangement

The illustrated transformation has been reported by Aube and co-workers in conjunction with an ongoing synthesis of the tetracyclic alkaloid stenine(*Angew. Chem. Int. Ed.* **2002**, *41*, 4316).



stenine

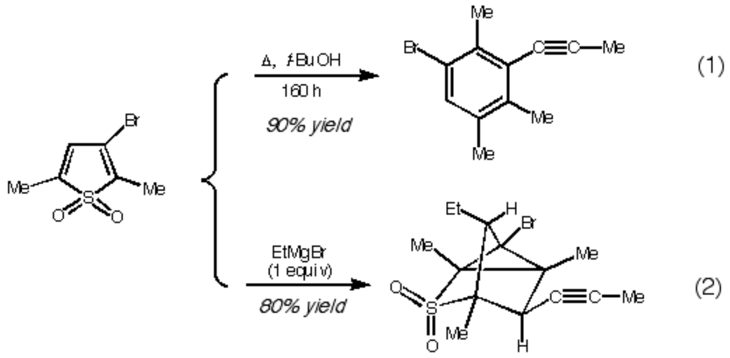


Provide a plausible mechanism for this reaction sequence. Your answer should include three-dimensional structures that accurately depict ground and transition state representations.

## Problem 73

Contributer: **David A. Evans**
Citation:
Keywords: Rearrangement

During the May 5th seminar of Professor S. Gronowitz at Harvard on the chemistry of thiophene-1,1-dioxides, several mechanistically intriguing transformations were presented (eq 1, 2).



**Part A.** Provide a plausible mechanism for the transformation illustrated in eq 1.

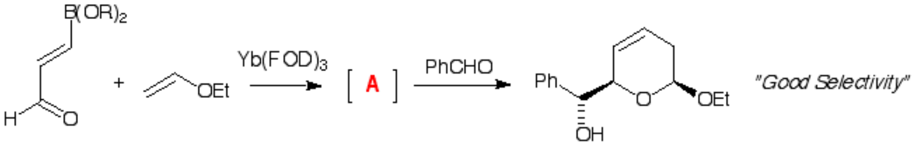
**Part B.** Provide a plausible mechanism for the transformation illustrated in eq 62

**Commentary:** Please take care with the rendering of structures in your mechanisms. They should be unambiguously drawn.

## Problem 78

Contributer: **David A. Evans**
Citation: *Chem. Commun.* **2003**, 276
Keywords: Rearrangement

The illustrated diastereoselective dihydropyran synthesis has been reported by Deligny and co-workers (*Chem Commun.* **2003**, 276).

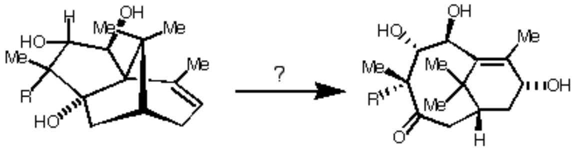


Provide a plausible mechanism for this reaction sequence. Your answer should include three-dimensional structures that accurately depict ground and transition state representations.

## Problem 79

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1988**, *110*, 6558
Keywords: Rearrangement

In a synthesis of taxusin, the pivotal reaction(s) which generated the bicyclo [5.3.1.]-undecane ring system charactertistic of this family of terpenoids are illustrated below. Given the illustrated transformation, what specific reagents would you employ to carry out this process.

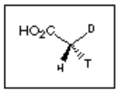


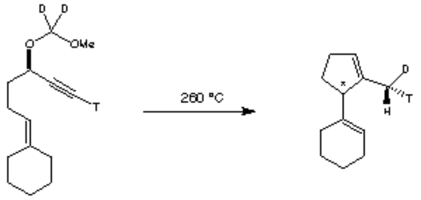
Holton & Co-workers, *JACS*, **110**, 6558 (1988).

## Problem 82

Contributer: **David A. Evans**
Citation: *Chem. Commun.* **1975**, 921
Keywords: Rearrangement

Chiral methyl groups are commonly used to probe the stereochemical outcome of biological reaction mechanisms. Many interesting strategies have been developed to synthesize chiral methyl groups in high enantiomeric excess. The first approach, designed by Arigoni (*Chem. Commun.* 1975, 921), is illustrated below.



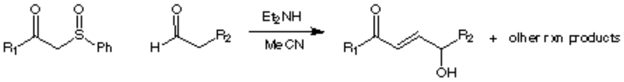


Provide a mechanism for the following transformation that accounts for the (H,D,T) stereochemistry of the chiral methyl group. You do not need to account for the stereochemistry at the starred carbon (it was not determined by the investigators).

## Problem 83

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2001**, *66*, 1228
Keywords: Rearrangement

The illustrated Knovenagel-type condensation recently reported by Nokami et al. (*J. Org. Chem.* 2001, *66*, 1228) should prove to be a generally useful transformation.

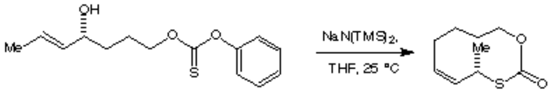


In the space below, provide a mechanism for the indicated transformation.

## Problem 84

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* , *31*, 5471
Keywords: Rearrangement

The illustrated transformation was reported by Kurihara et al. (*Tet Lett.* 1990, *31*, 5471).

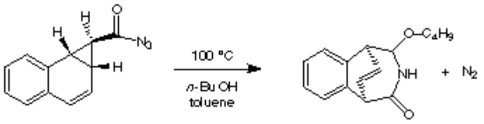


Provide a mechanism for the indicated transformation that accounts for the overall stereochemical outcome of the reaction. Three dimensional drawings should be provided to support your answer.

## Problem 85

Contributer: **David A. Evans**
Citation: *Tetrahedron* **1959**, *5*, 53
Keywords: Rearrangement

In a classic thermal transformation first disclosed by Doering and Goldstein (*Tetrahedron*, 1959, *5*, 53), the acyl azide below was heated in the presence of butanol to afford a 1:1 mixture of diastereomers. Later studies by Müller and coworkers determined that enantiomerically pure starting material provides enantiomerically pure lactam product.

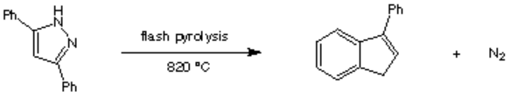


Please provide a mechanism of this transformation while paying particular attention to the stereochemistry of the process.

## Problem 88

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1998**, *63*, 8188
Keywords: Rearrangement

Please provide a mechanism for the following high temperature reaction that was reported by Yranzo and co-workers (*J. Org. Chem.* 1998, *63*, 8188).

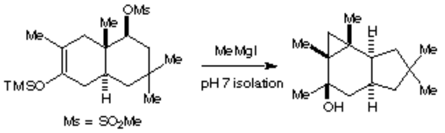


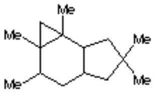
Draw a plausible mechanism for the transformation to the major product isomer. *Do not invoke any radical intermediates in your answer.*

## Problem 90

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2001**, *66*, 2350
Keywords: Rearrangement

The synthesis of the marasmane sesquiterpene skeleton has been to topic of several research groups. In a recent paper (*J. Org. Chem.* 2001, *66*, 2350) de Groot et al. have developed an ingeneous approach to the assemblage of this ring system.





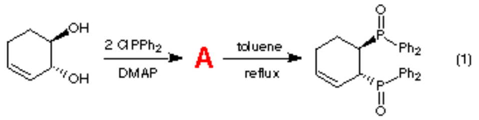
marasmane skeleton

In the space below, provide a mechanism for the indicated transformation.

## Problem 96

Contributer: **David A. Evans**
Citation: *Angew. Chem.* **2001**, *40*, 1235
Keywords: Rearrangement

Frequently, the limiting factor in the widespread use of chiral catalysts is the efficiency of the chiral ligand synthesis. Knochel (*Angew. Chem. Int. Ed.* 2001, *40*, 1235) has developed an efficient rhodium catalyst for asymmetric Hydroboration. The key step in the synthesis of the chiral ligand is illustrated below (eq 1).

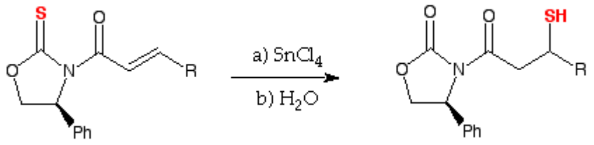


Please provide a mechanism for the reaction in equation 1 and identify the intermediate A.

## Problem 103

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **2003**, *44*, 1129-1132
Keywords: Rearrangement

The following intramolecular sulfur transfer process was recently reported by Ortiz (*Tetrahedron Lett.* **2003**, *44*, 1129-1132) and earlier by Palomo (*JACS* **2001**, *123*, 5602). Predict the stereochemical outcome of this transformation.

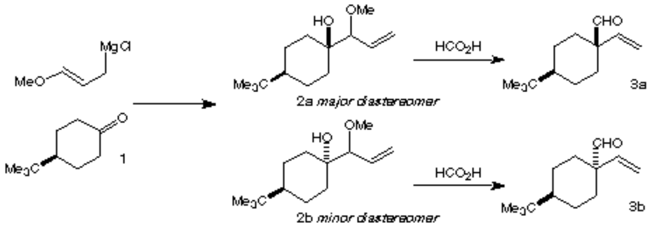


diastereoselection ~98:2 (72%)

## Problem 104

Contributer: **David A. Evans**
Citation: *Evans, Unpublished Results*
Keywords: Rearrangement

The indicated allylmetal nucleophile adds regioselectively to the indicated cyclohexanone derivative 1 to afford the tertiary alcohols 2a and 2b having the indicated stereochemistry (Evans & Andrews, *Unpublished*, 1974). These adducts may be individually rearranged to the indicated aldehydes 3a and 3b with complete control of stereochemistry. This set of transformations readily provides access to functionalized quaternary centers.

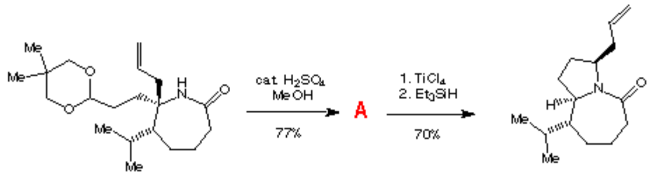


Provide a mechanism for the transformation of 2a into 3a that is consistent with the experimental observations. Where appropriate, provide three-dimensional drawings to reinforce your answer.

## Problem 107

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2001**, *66*, 7751
Keywords: Rearrangement

In Heathcock's recent synthetic approach to the *Stemona* alkaloids, an interesting series of transformations were used (Heathcock, JOC, 2001, *66*, 7751).

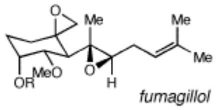


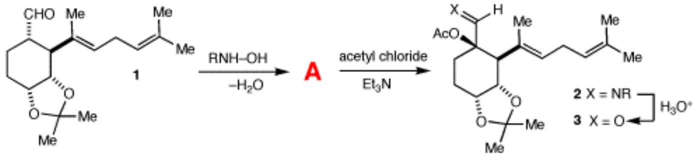
Please provide a mechanism for each reaction and identify the structure of intermediate A.

## Problem 108

Contributer: **David A. Evans**
Citation: *Angew. Chem.* **1999**, *38*, 971
Keywords: Rearrangement

The fumagillin natural products possess several interesting biological properties including antibiotic activity against *Staphylococcus aueress.* In Sorensen's recent synthesis of fumagillol (*Angew. Chem, Int. Ed.* **1999**, *38*, 971), intermediate **1** was transformed into its a-oxygenated counterpart **3** through the indicated reaction sequence.



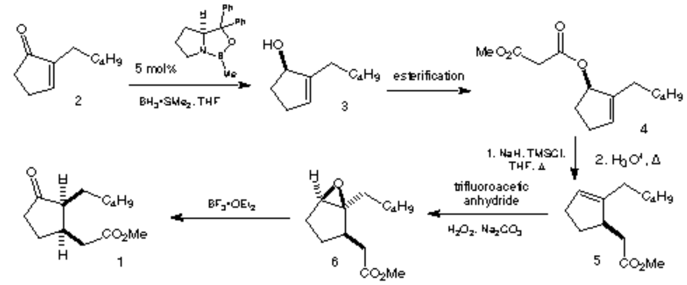


In the space below, identify the structure of intermediate **A** and provide a mechanism for the transformation of **1** into **2**.

## Problem 116

Contributer: **David A. Evans**
Citation: *Angew. Chem.* **2000**, *39*, 569-573
Keywords: Rearrangement

In their total synthesis of (+)-methyl epijasmonate (1), Fehr and co-workers (*Angew. Chem Int. Ed.* 2000, *39*, 569-573) deftly relay stereochemical relationships about the cyclopentane skeleton. Their synthetic sequence is outlined below.



Part A. Provide a clear 3-dimensional drawing which clearly illustrates the control elements for the reduction of 2 to 3.

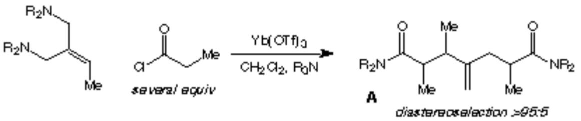
Part B. Provide a mechanism for the transformation of malonate 4 to methyl ester 5.

Part C. Discuss the stereochemical attributes of the epoxidation of 5 to give 6. *Hint: It should be noted here that other epoxidizing agents such as MCPBA are far less stereoselective.*

## Problem 117

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2001**, *123*, 2448
Keywords: Rearrangement

In a recent article, MacMillan and Yoon (*JACS* 2001, *123*, 2448) reported the complex rearrangement illustrated below.



Part A. Provide a mechanism for this overall transformation. In answering this question, you should illustrate those transition states where stereocenters are generated and where stereochemcal information is relayed.

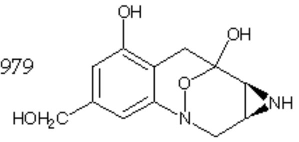
Part B. From your answer in Part A, illustrate the stereochemical relationships in the diamide product A.

## Problem 118

Contributer: **David A. Evans**
Citation: *Angew. Chem.* **2002**, *41*, 4688
Keywords: Rearrangement

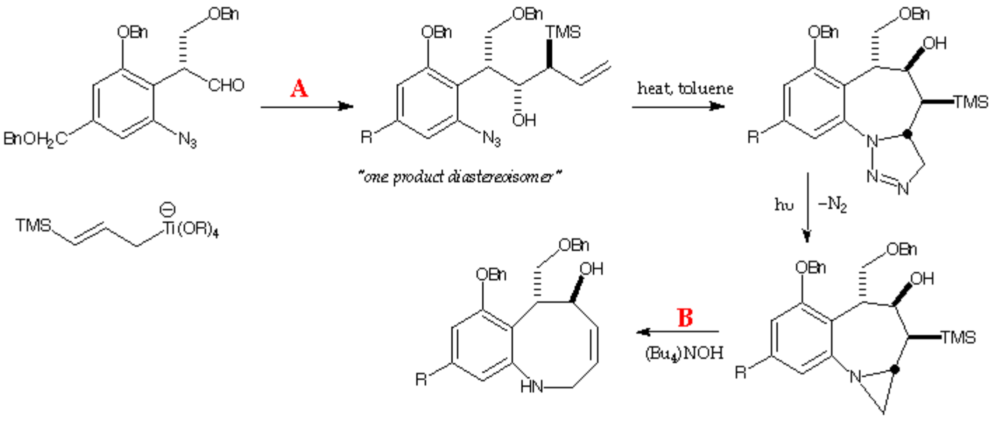
A stereoselective synthesis of the antitumor alkaloid FR66979 has been reported by Ciufolini (*Angew. Chem. Int. Ed.* **2002**, *41*, 4688). This question pertains to the transformations labeled **A** and **B**.

FR66979



**Part A.** Rationalize the stereochemical outcome of this diastereoselective carbonyl addition.

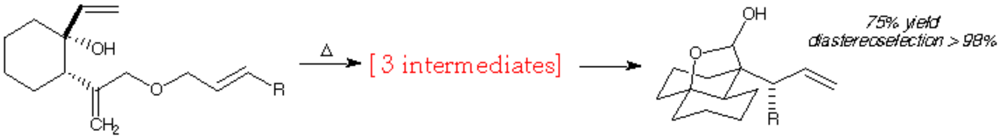
**Part B.** Provide a deteiled mechanism for this transformation.



## Problem 119

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2002**, *4*, 1371
Keywords: Rearrangement

Barriault has reported an interesting thermally initiated reaction cascade (*Org. Lett* **2002**, *4*, 1371). One of his reported transformations is illustrated below. The paper includes ten related examples.

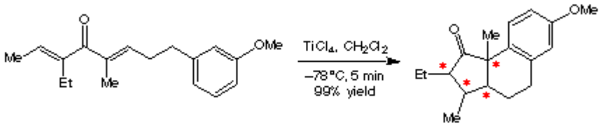


Provide a detailed mechanism for this reaction cascade. Your answer should include three-dimensional structures that accurately depict ground and transition state representations.

## Problem 122

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2001**, *3*, 3033-3035
Keywords: Rearrangement

The interesting transformation illustrated below was recently reported by F. West and co-workers (*Org. Lett.* 2001, 3, 3033-3035). The pivotal reaction upon which this transformation was designed is a pericyclic process that affords a pivotal element of stereocontrol.



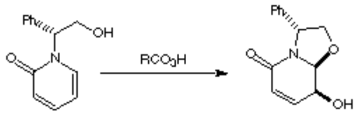
Part A. Identify the pericyclic process that intervenes in the illustrated transformation and illustrate the relative configuration(s) stereocenter(s) that are generated.

Part B. Provide a mechanism for the overall transformation. Since stereochemical issues are at stake, carefully rendered 3-D conformational drawings should be incorporated into your answer.

## Problem 125

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2001**, *3*, 3257-3260
Keywords: Rearrangement

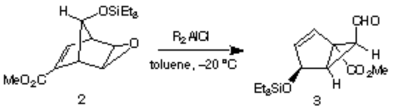
The following reaction was recently reported by Amat and co-workers (*Org. Lett.* 2001, *3*, 3257-3260). Provide a mechanism for the this transformation which is consistent with the product stereochemistry. Since stereochemical issues are at stake, carefully rendered 3-D conformational drawings should be incorporated into your answer.



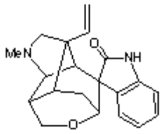
## Problem 139

Contributer: **David A. Evans**
Citation: *Angew. Chem.* **2000**, *39*, 4073
Keywords: Rearrangement

Fukuyama has recently reported an elegant synthesis of gelsamine (1) (*Angew. Chem. Int. Ed.* 2000, *39*, 4073). During the course of the synthesis, the rearrangement of 2 → 3 was reported (eq 1).



(1)



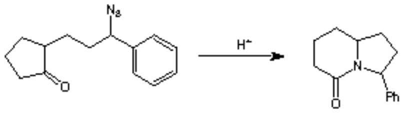
*gelsamine (1)*

Provide a concise mechanism for this reaction in the space below.

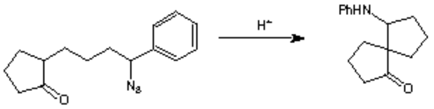
## Problem 141

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2001**, *66*, 886
Keywords: Rearrangement

Aube has recently reported the transformations illustrated below (*J. Org. Chem.* 2001, 66, 886-889). In this study he has documented that the observed product is dependent on the tether length between the azide and carbonyl functional groups.



(eq 1)



(eq 2)

Part A. Provide a mechanism for the transformation illustrated in Eq 1.

Part B. Provide a mechanism for the transformation illustrated in Eq 2.

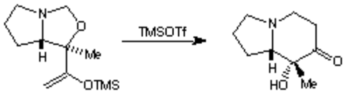
Part C. Briefly rationalize the difference in reactivity.

## Problem 142

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1992**, *57*, 1179
Keywords: Rearrangement

During the course of the Overman synthesis of pumilotoxin (*J. Org. Chem.* 1992, *57*, 1179) the indicated transformation was carried out with the expectation that the bicyclic ketone 2 would be enantiopure since the starting amine 1 was enantiomerically pure. Surprisingly, product 2 was obtained as a racemate.

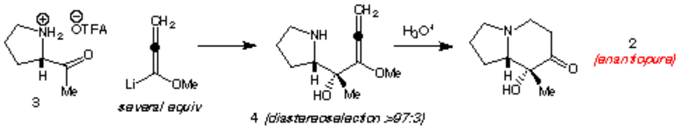
1 *(enantiopure)*



2 *(racemic)*

Part A. Provide a mechanism for this transformation that accounts for the illustrated stereochemical outcome.

The revised synthesis of enantiomerically pure 2 is illustrated below (*J. Org. Chem.* 1992, *57*, 1179). Addition of 3 to several equivalents of the illustrated allenyllithium reagent afforded carbonyl adduct 4 as a single diastereomer. This intermediate was then transformed into enantiopure 2 under acidic conditions.



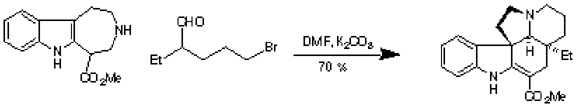
Part B. Provide an explanation for the high level of stereocontrol that is observed in the carbonyl addition step. A three dimensional drawing of the carbonyl addition transition state is requested in conjunction with this answer.

Part C. Provide a mechanism for the transformation of 4 to 2.

## Problem 145

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1978**, *43*, 3705
Keywords: Rearrangement

Martin Kuhne has described a biomimetic approach to the construction of the aspidosperma alkaloid skeleton (*J. Org. Chem.* 1978, 43, 3705). One of the reactions developed in his laboratory is illustrated below.

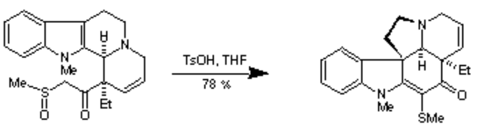


Provide a detailed mechanism for the illustrated transformation.

## Problem 146

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1985**, *50*, 961
Keywords: Rearrangement

An interesting rearrangement which also results in the construction of this same ring system (Question 4) has been reported by Langlois & coworkers (*J. Org. Chem.* 1985, 50, 961). This rearrangement is illustrated below.



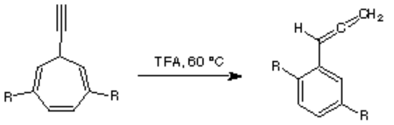
Provide a detailed mechanism for the illustrated transformation. Use three-dimensional representations, where relevant, to illustrate the stereochemical aspects of the individual steps.

## Problem 147

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2000**, *2*, 3011
Keywords: Rearrangement

Kitagawa and coworkers (Org. Lett. 2000, 2, 3011) have recently described the trifluoroacetic acid (TFA) catalyzed rearrangement illustrated below.

| substituent | rel rate |
|---|---|
| R = H | 1 |
| R = t-Bu | 370 |



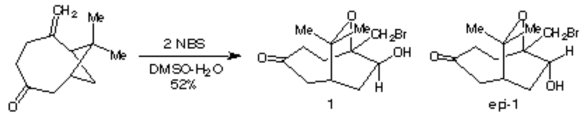
Part A. Provide a concise mechanism for this reaction in the space below.

Part B. Please rationalize the rate difference for the two substrates. *Hint: In addressing this final point I recommend that you build a model of the starting cycloheptatriene.*

## Problem 148

Contributer: **David A. Evans**
Citation: *SynLett* **1997**, 1161
Keywords: Rearrangement

Mehta and coworkers (*SynLett* 1997, 1161) have recently described the *N*-bromosuccinimide (NBS) promoted rearrangement illustrated below. While the product was assigned the exo stereochemistry as illustrated in 1, DAE feels that the epi-1 structure cannot be ruled out.

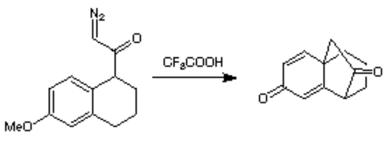


Provide a concise mechanism for this reaction in the space below.

## Problem 150

Contributer: **David A. Evans**
Citation:
Keywords: Rearrangement

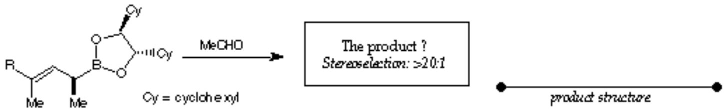
Provide a concise mechanism for the indicated reaction in the space below.



## Problem 152

Contributer: **David A. Evans**
Citation: **1991**, 1203
Keywords: Rearrangement

The following stereoselective transformation has been reported by Hoffmann (*Liebig's Ann. Chem.* 1991, 1203). Provide the stereostructure of the major product and rationalize the stereochemical outcome of the process.

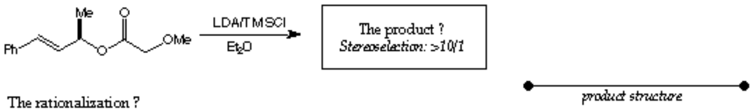


The rationalization ?

## Problem 153

Contributer: **David A. Evans**
Citation:
Keywords: Rearrangement

Provide the stereostructure of the major product of the indicated transformation, and rationalize the stereochemical outcome of the process.

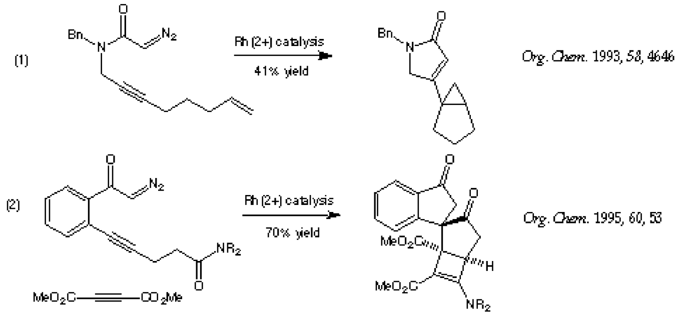


The rationalization ?

## Problem 169

Contributer: **David A. Evans**
Citation:
Keywords: Rearrangement

Padwa has reported the rhodium-catalyzed complex cascade processes illustrated below (Eq 1, 2). At issue here is the consequence of the reaction of a rhodium carbenoid with a triple bond, a process that we did not directly discuss. If you deduce the mechanism of the transformation in Eq 1, the more complex variant illustrated in Eq 2 will be soluble.



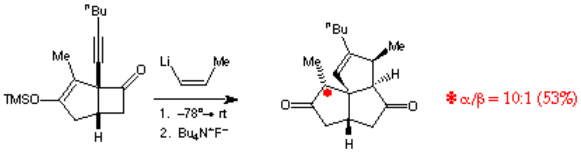
Part A. Provide a concise mechanism for the transformantion illustrated in Eq 1.

Part B. Provide a concise mechanism for the transformantion illustrated in Eq 2.

## Problem 170

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2000**, *65*, 8564
Keywords: Rearrangement

Moore has recently reported the illustrated reaction cascade which rapidly leads to the assemblage of the illustrated tricyclic diketone (*J. Org. Chem.* 2000, 65, 8564).

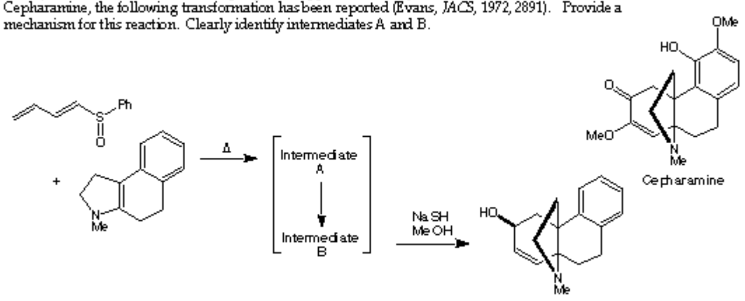


Provide a concise mechanism for the illustrated reaction sequence in the space below.

## Problem 175

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1972**, 2891
Keywords: Rearrangement

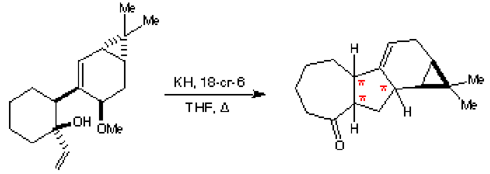
In conjunction with efforts to develop a general approach to the synthesis of the hasubanan alkaloid Cepharamine, the following transformation has been reported (Evans, *JACS*, 1972, 2891). Provide a mechanism for this reaction. Clearly identify intermediates A and B.



## Problem 176

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1989**, 5205
Keywords: Rearrangement

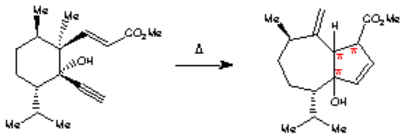
Provide a mechanism for the following transformation that predicts the stereochemistry at the starred (*) carbon atoms (Paquette, *JOC*, 1989, 5205).



## Problem 177

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1998**, *39*, 4133
Keywords: Rearrangement

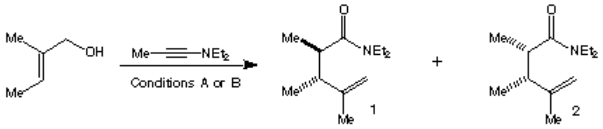
Provide a mechanism that predicts the observed stereochemistry at the starred (*) carbon atoms (Rajagopalan, *Tetrahedron Lett.* 1998, 39, 4133). Draw the starting material, each intermediate, and the product clearly in 3D.



## Problem 178

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1979**, 882
Keywords: Rearrangement

Provide a mechanistic rationale for the following observations (Bartlett, P. A. *JOC*, 1979, 882). Note: the products were shown to be stable to the reaction conditions.



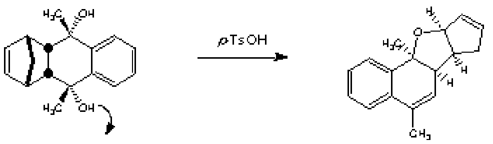
Conditions A: Steady addition of ROH to ynamine.
Conditions B: ROH and ynamine stirred in the presence of a catalytic amount of $BF_3$•etherate in benzene for 4 days.

| Conditions | 1 : 2 |
|---|---|
| A | 10:1 |
| B | 1:10 |

## Problem 183

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1990**, 5357
Keywords: Rearrangement

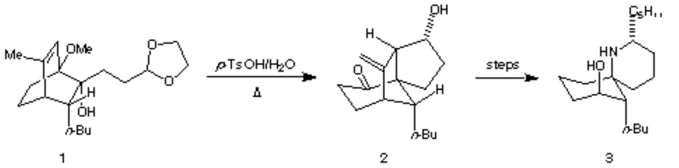
Provide a mechanism for the following transformation (Coxon, *Tetrahedron* Lett. 1990, 5357).



## Problem 184

Contributer: **David A. Evans**
Citation: *Chem. Commun.* **1997**, 2263
Keywords: Rearrangement

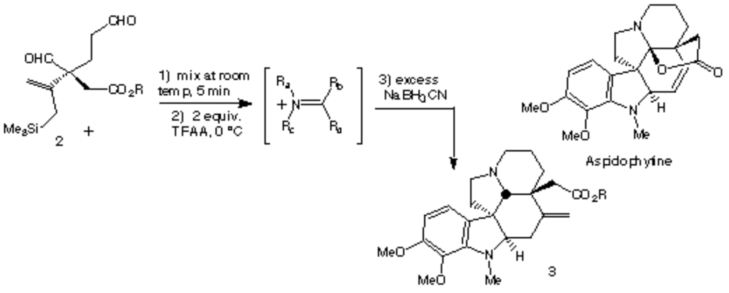
The key step in Kim's synthesis of perhydrohistrionicotoxin, 3, was the conversion of intermediate 1 to ketone 2 in a single acid-catalyzed transformation (*Chem. Commun.*, 1997, 2263). Provide a mechanism for the conversion of 1 to 2 that accounts for the observed stereochemistry.



## Problem 185

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1999**, *121*, 6771
Keywords: Rearrangement

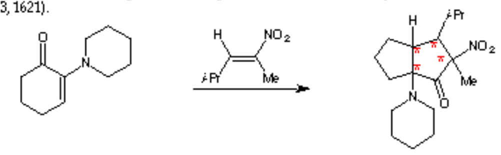
During Corey's recent synthesis of Aspidophytine (*JACS*, 1999, *121*, 6771), the pivotal intermediate 3 was assembled by the union of 1 and 2 under the specified conditions. Provide a mechanism for this single-pot transformation.



## Problem 188

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1983**, 1621
Keywords: Rearrangement

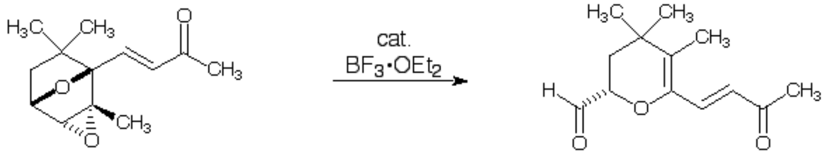
Provide a mechanism for the following reaction that predicts the stereochemistry at the starred (*) carbon atoms (Valentin, *TL*, 1983, 1621).



## Problem 192

Contributer: **David A. Evans**
Citation: *Chem. Commun.* **1992**, 342
Keywords: Rearrangement

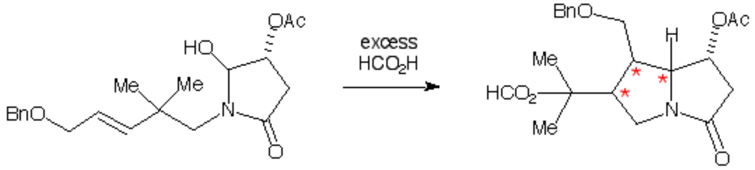
Provide a mechanism for the following reaction (*Chem. Comm*, **1992**, 342).



## Problem 193

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1985**, 235
Keywords: Rearrangement

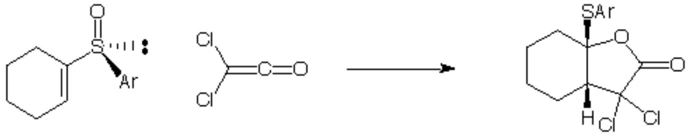
Provide a mechanism for the indicated transformation that predicts the observed stereochemistry at the three starred (*) carbon atoms (*JOC*, **1985**, 235).



## Problem 195

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1984**, 7643
Keywords: Rearrangement

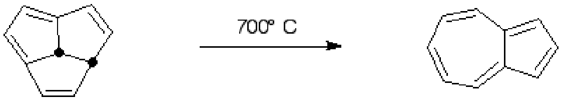
Provide a mechanism for the indicated transformation that accounts for the observed stereochemical outcome (*JACS*, **1984**, 7643).



## Problem 198

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1973**, 2724
Keywords: Rearrangement

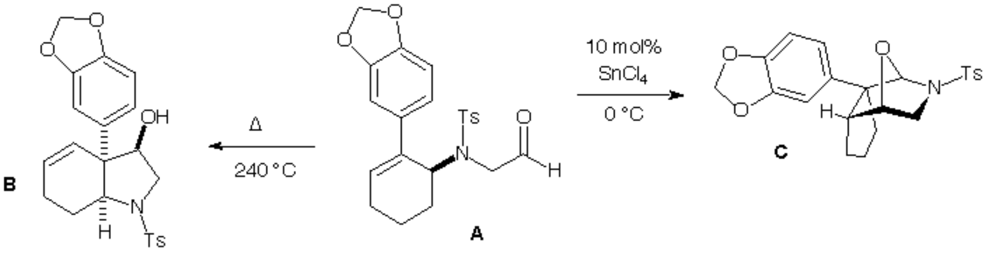
Provide a mechanism for the thermal conversion of triquinacene to azulene (*JACS*, **1973**, 2724).



## Problem 203

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1998**
Keywords: Rearrangement

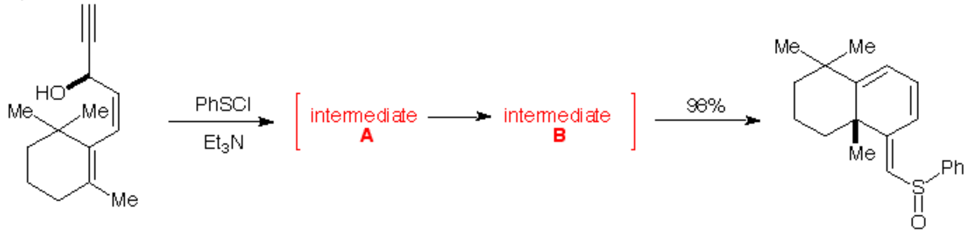
Provide mechanisms that account for the stereoselective formation of the products obtained by treatment of aldehyde **A** to the conditions shown below. Briefly comment on the difference in reactivity under the two sets of conditions (*JOC*, **1998**, 7586).



## Problem 212

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1985**, *107*, 1034
Keywords: Rearrangement

Provide a mechanism for the following transformation. Identify **A** and **B** in your reaction sequence. (Okamura JACS **1985**, *107*, 1034).

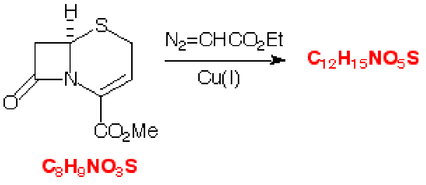


## Problem 213

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1972**, 2923
Keywords: Rearrangement

Based on the knowledge that you have acquired in this course, predict the product of the reaction and provide a mechanism for the transformation. In addition to the molecular formula of the product, the NMR spectrum indicated the presence of three olefinic H's, one OMe fragment, and one OEt fragment (*Tet. Lett.* **1972**, 2923).

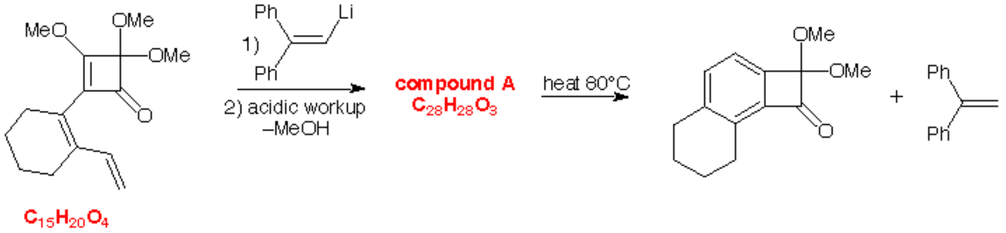
To receive full credit, you must also illustrate how any new stereochemical relationships are created.



## Problem 215

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1999**, *64*, 2170
Keywords: Rearrangement

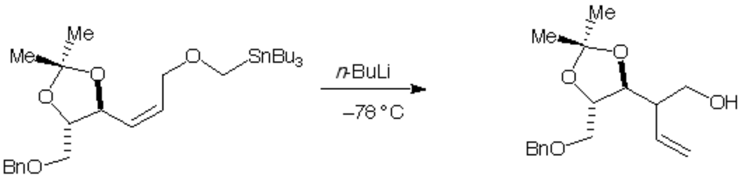
Provide a mechanism for the following set of transformations (*J. Org. Chem.* **1999**, *64*, 2170). It should be noted that compound **A** exhibits a strong carbonyl frequency in the infrared spectrum. Clearly indicate the structure of compound **A** and the relative stereochemistry of any chiral intermediates.



## Problem 216

Contributer: **David A. Evans**
Citation: *Tetrahedron* **1999**, *55*, 13369
Keywords: Rearrangement

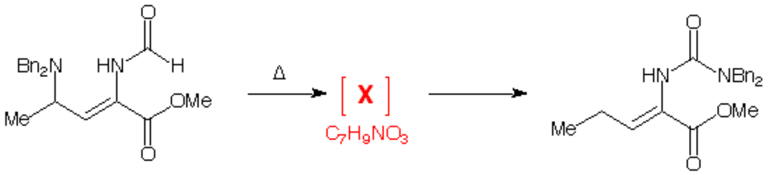
Provide a mechanism for this rearrangement that predicts the major product diastereomer (*Tetrahedron*, **1999**, *55*, 13369).



## Problem 217

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1993**, 579
Keywords: Rearrangement

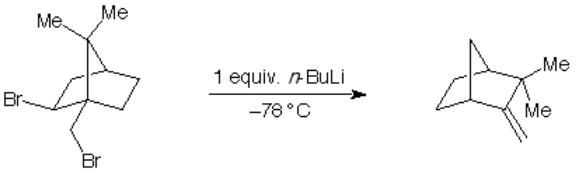
Provide a mechanism for the following reaction. The reaction was shown to proceed through isocyanate (RNCO) **X**. Identify **X** (Kende, *TL*, **1993**, 579).



## Problem 218

Contributer: **David A. Evans**
Citation: *Angew. Chem.* **1998**, 3173
Keywords: Rearrangement

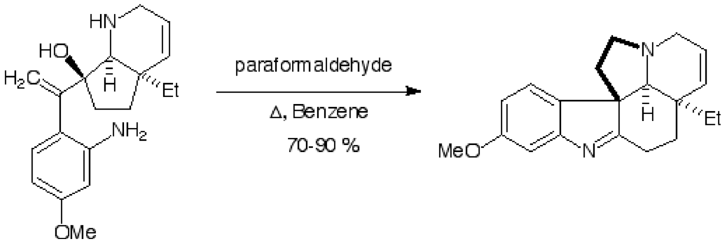
Provide a plausible mechanism for the following anionic rearrangement (Schlosser, *ACIE*, **1998**, 3173).



## Problem 225

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1983**, *48*, 2685
Keywords: Rearrangement

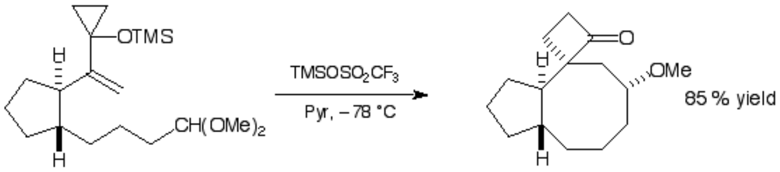
One of the most innovative reactions which results in the construction of the aspidosperma alkaloid skeleton has recently been reported by Professor L. Overman (*JOC* **1983**, *48*, 2685). Provide a concise mechanism for this reaction.



## Problem 230

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1986**, *110*, 6556
Keywords: Rearrangement

Write a plausible mechanism for the reaction illustrated below. Where stereochemistry is an issue, draw the conformation of the reacting entity which illustrates the relationship between chiral and prochiral centers.

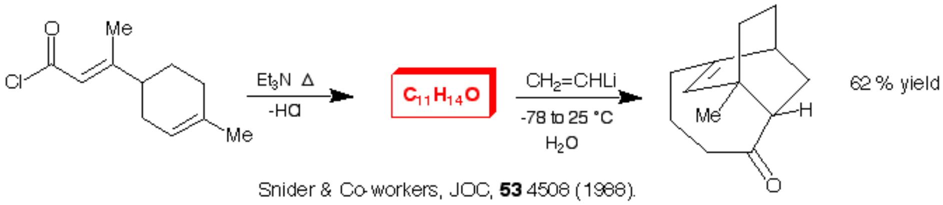


Trost & Co-workers, *JACS*, **110**, 6556 (1988).

## Problem 231

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1988**, *53*, 4508
Keywords: Rearrangement

Write a plausible mechanism for the two-step illustrated below. Where stereochemistry is an issue, draw the conformation of the reacting entity which illustrates the relationship between chiral and prochiral centers.

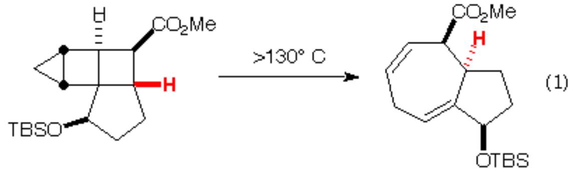


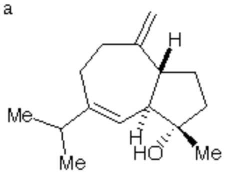
Snider & Co-workers, JOC, **53** 4508 (1988).

## Problem 233

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2001**, *123*, 5152
Keywords: Rearrangement

Snapper and co-workers have reported an approach to the [5.3.0] ring system that is commmon to a number of sesquiterpenes(*JACS* **2001**, *123*, 5152). One cited example is alismol whose structure is provided for reference. Upon thermolysis, the illustrated tetracyclic ester is transformed into the illustrated bicyclic ring system in 64% yield (eq 1).





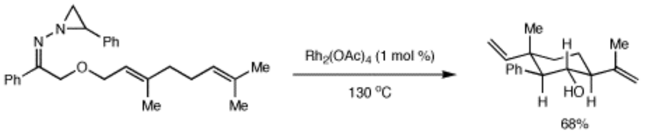
Alismol

Provide a plausible mechanism for this transformation. Your answer should include an explanatin of the somewhat unusual stereochemical inversion of the center carrying the flagged "red" hydrogen.

## Problem 234

Contributer: **Carl A. Morales**
Citation: *J. Am. Chem. Soc.* **2002**, *124*, 12426
Keywords: Rearrangement

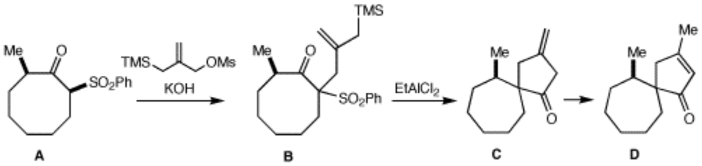
Recent work from the Stoltz labs on non-carbonyl-stabilized metallocarbenoids has fostered "the development of a tandem rhodium-catalyzed Bamford-Stevens/thermal aliphatic Claisen rearrangment sequence." Please demonstrate your appreciation for this methodology by providing a plausible mechanism for the impressive transformation below, noting the relative stereochemistry of the product and the fact that styrene is a byproduct of the reaction.



## Problem 237

Contributer: **Carl A. Morales**
Citation: *J. Am. Chem. Soc.* **1983**, *105*, 4349
Keywords: Rearrangement

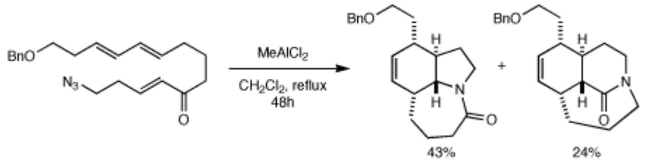
The following two step reaction sequence converts starting material **A** into **C** where under the conditions of the second step, **C** is isomerized to product **D**. Provide mechanisms for the conversion of **A** to **B** and for **B** to **C** and predict the stereochemistry of **B** and **C** using clear 3D representations to justify your choice.



## Problem 240

Contributer: **Carl A. Morales**
Citation: *Angew. Chem.* **2002**, *41*, 4492
Keywords: Rearrangement

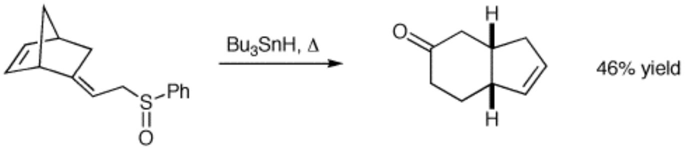
In a recent report of a formal synthesis of stenine, researchers reported a tandem polycyclization which afforded the following major and minor products. Please propose a mechanism for this transformation which accounts for both products, their relative stereochemistry, and their relative distribution.



## Problem 241

Contributer: **David A. Evans**
Citation: *Angew. Chem.* **2002**, *41*, 4323
Keywords: Rearrangement

Renaud has disclosed an interesting reaction cascade (*Angew. Chem. Int. Ed.* **2002**, *41*, 4323). One of the reported transformations is illustrated below. The paper includes six related examples.

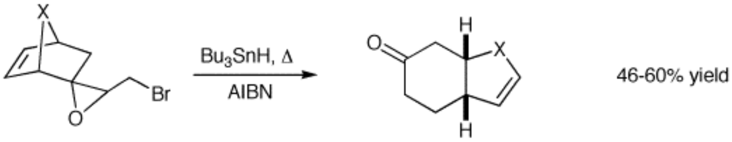


Provide a plausible mechanism for this reaction cascade. Your answer should include three-dimensional structures that accurately depict ground and transition state representations.

## Problem 242

Contributer: **David A. Evans**
Citation: *Angew. Chem.* **2002**, *41*, 4321-4323
Keywords: Rearrangement

Renaud has disclosed an interesting reaction cascade (*Angew. Chem. Int. Ed.* **2002**, *41*, 4321). One of the reported transformations is illustrated below. The paper includes related examples.

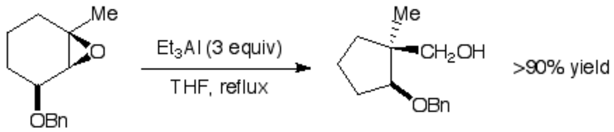


Provide a plausible mechanism for this reaction cascade. Your answer should include three-dimensional structures that accurately depict ground and transition state representations.

## Problem 243

Contributer: **David A. Evans**
Citation: *Chem. Commun.* **2003**, 798
Keywords: Rearrangement

The following ring contraction has been reported by Li and co-workers (*Chem. Commun.* **2003**, 798). One of the reported transformations is illustrated below. The paper includes nine related examples.

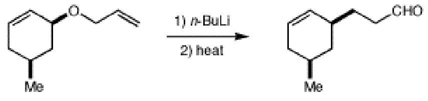


Provide a plausible mechanism for this reaction cascade. Your answer should include three-dimensional structures that accurately depict ground and transition state representations.

## Problem 258

Contributer:
Citation: *Tetrahedron Lett.* **1982**, *23*, 3931
Keywords: Rearrangement

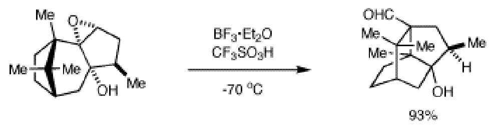
Provide a mechanism for the following transformation. Include the stereochemistry of all intermediates and provide 3D drawings of all transition states.



## Problem 260

Contributer: **Carl A. Morales**
Citation: *Strategies & Tactics in Org. Syn.* **1991**, *3* , 165-198
Keywords: Rearrangement

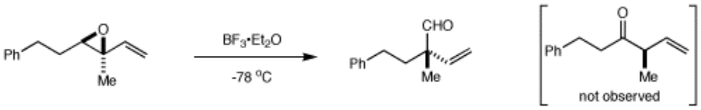
Using 3D representations, provide a mechanism for the transformation below.



## Problem 261

Contributer: **Carl A. Morales**
Citation: *J. Am. Chem. Soc.* **1995**, *117*, 7379
Keywords: Rearrangement

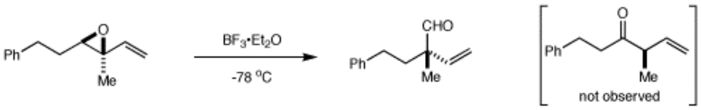
Please provide a mechanism for the following transformation that clearly explains the exclusive formation of the indicated aldehyde product and the lack of ketone.



## Problem 262

Contributer: **Carl A. Morales**
Citation: *J. Am. Chem. Soc.* **1995**, *117*, 7379
Keywords: Rearrangement

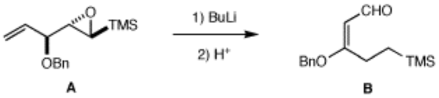
Please provide a mechanism for the following transformation that clearly explains the exclusive formation of the indicated aldehyde product and the lack of ketone.



## Problem 264

Contributer: **Carl A. Morales**
Citation: *J. Org. Chem.* **1996**, *61*, 9065
Keywords: Rearrangement

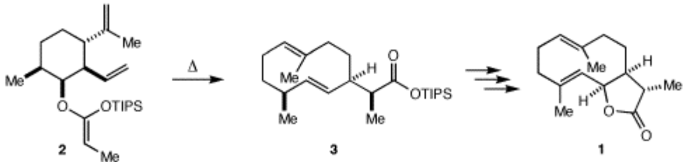
In a recent study, the authors began life with chiral epoxide **A** and obtained aldehyde **B** following the conditions below. Provide a mechanism that accounts for this stereo-destructive process. You do not have to explain the double bond geometry in the product.



## Problem 265

Contributer: **Carl A. Morales**
Citation: *J. Org. Chem.* **1986**, *51*, 5503
Keywords: Rearrangement

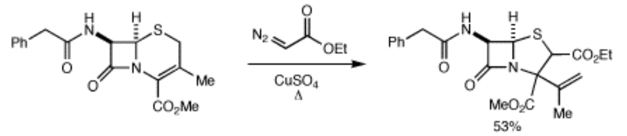
The following reaction was a key step in the enantioselective synthesis of (+)-dihydrocostunolide **1**. Provide a reasonable mechanism for the conversion of **2** to **3** using clear 3D representations.



## Problem 266

Contributer: **Carl A. Morales**
Citation: *Tetrahedron Lett.* **1972**, 2923
Keywords: Rearrangement

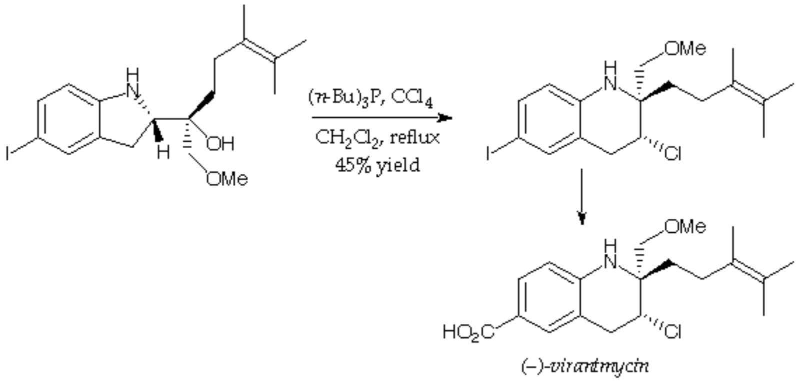
Provide a mechanism for the following transformation and predict the stereochemistry of the product (Yashimoto, M. *Tetrahedron Lett.* **1972**, 2923).



## Problem 279

Contributer: **Jake Janey**
Citation: *Angew. Chem.* **2003**, *42*, 2540-2543
Keywords: Rearrangement

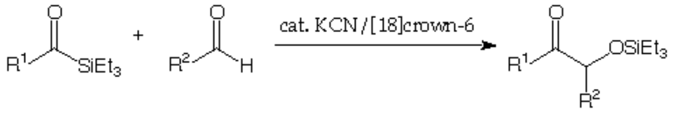
Kogen has reported an interesting rearrangement of indoline-2-methanol to 2,2,3-trisubstituted tetrahydroquinoline (*Angew. Chem. Int. Ed., Engl.* **2003**, *42*, 2540-2543). Along with numerous examples, they reported a synthesis of (–)-virantmycin. Propose a plausible mechanism for this rearrangement.



## Problem 280

Contributer: **Jake Janey**
Citation: *Angew. Chem.* **2003**, *42*, 2534-2536
Keywords: Rearrangement

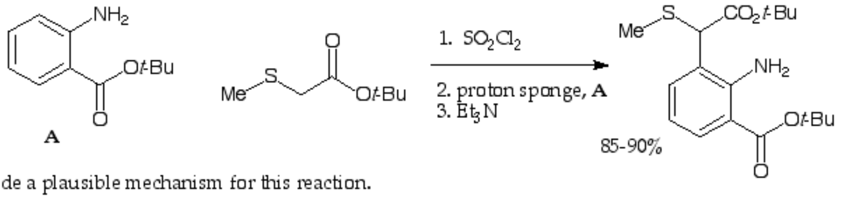
J. S. Johnson has reported a way of forming α-hydroxy ketones by a cross condensation of an aldehyde and an acylsilane catalyzed by KCN/[18]crown-6 (*Angew. Chem. Int. Ed., Engl.* **2003**, *42*, 2534). This reaction is quite general for forming a variety of α-hydroxy ketones. Provide a plausible mechanism for this cyanide catalyzed reaction.



## Problem 284

Contributer: **Karl Scheidt**
Citation: *J. Org. Chem.* **1990**, *55*, 1374-1375
Keywords: Rearrangement

In 1990, Johnson reported the useful reaction illustrated below for the synthesis of *o*-aminophenylacetates (*J. Org. Chem.* **1990**, *55*, 1374). This general process is generalizable to the ortho alkylation of aniline derivatives.

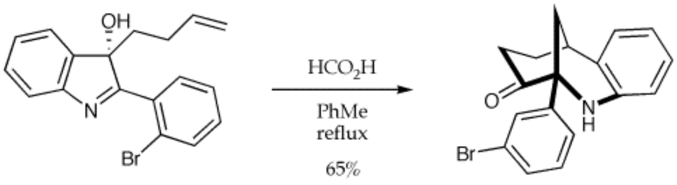


Provide a plausible mechanism for this reaction.

## Problem 286

Contributer: **Keith Woerpel**
Citation: *Organic Lett.* **2003**, *5*, 333
Keywords: Rearrangement

McWhorter reported a transformation of indolenes that is likely involved in the biosynthesis of biologically active indole diterpenes (*Org. Lett* **2003**, *5*, 333). Provide a mechanism for the illustrated transformation.

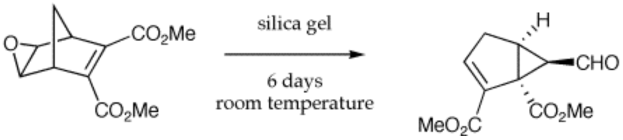


Provide a mechanism for the illustrated transformation.

## Problem 287

Contributer: **Keith Woerpel**
Citation: *J. Am. Chem. Soc.* **1994**, *116*, 3290
Keywords: Rearrangement

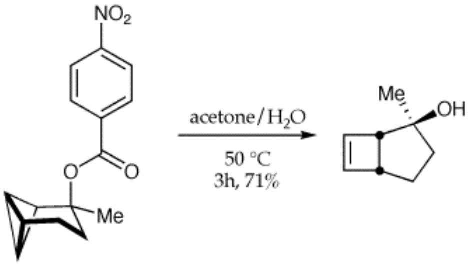
Provide a mechanism for the illustrated transformation, and rationalize the stereochemistry (S. Niwayama, S. Kobayashi *J. Am. Chem. Soc.* **1994,** *116*, 3290).



## Problem 289

Contributer: **Keith Woerpel**
Citation: *J. Org. Chem.* **1977**, *42*, 363
Keywords: Rearrangement

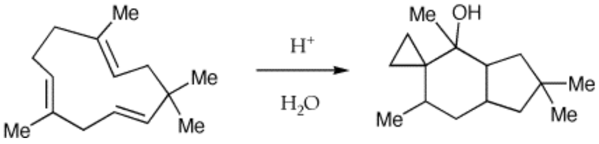
Provide a mechanism for the following transforrmation (K. Yano, K. Yoshida *J. Org. Chem.* **1977**, *42*, 363). The paper describes another related example as well as kinetic data for these reactions.



## Problem 291

Contributer: **Keith Woerpel**
Citation: *Tetrahedron Lett.* **1995**, *36*, 1989
Keywords: Rearrangement

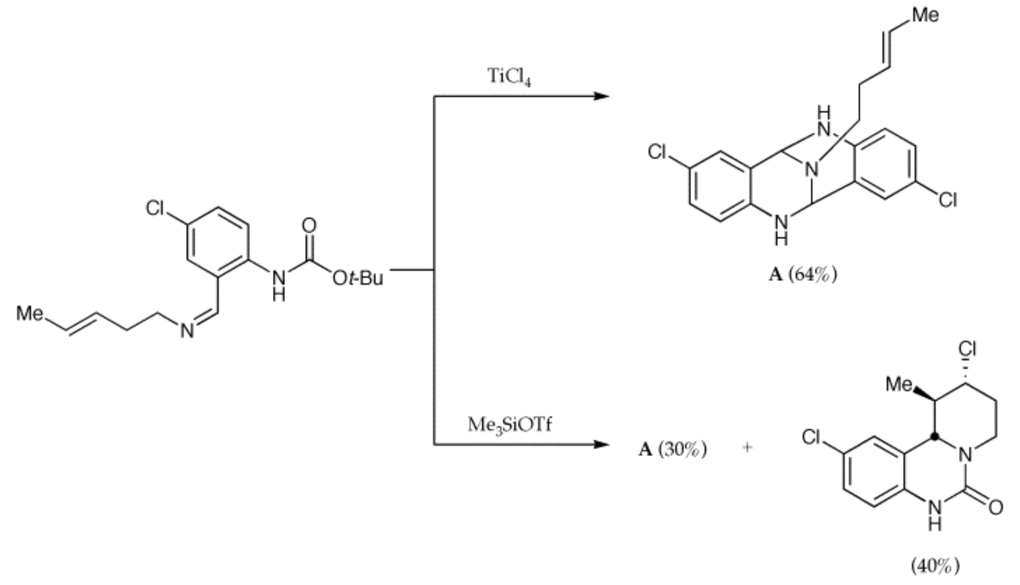
The biosynthesis of a family of sesquiterpenes, the pterosins, are believed to involve acid-catalyzed rearrangements. For example, the reaction shown below is believed to be part of the biosynthetic pathway. This transformation is part of Padwa's paper describing approaches to the synthesis of these natural products (A. Padwa *Tetrahedron Lett.* **1995**, *36*, 1989). Provide a mechanismfor this reaction.



## Problem 292

Contributer: **Keith Woerpel**
Citation: *Tetrahedron Lett.* **1998**, *39*, 7239
Keywords: Rearrangement

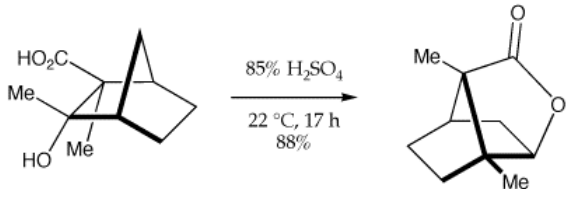
Provide a mechanism for the following transformation (J. Aubé, *Tetrahedron Lett.* **1998**, *39*, 7239). Your mechanism should account for stereochemistry as well as the different outcomes depending upon Lewis acid.



**Problem 295**

Contributer: **Keith Woerpel**
Citation: *J. Org. Chem.* **1971**, *36*, 2324
Keywords: Rearrangement

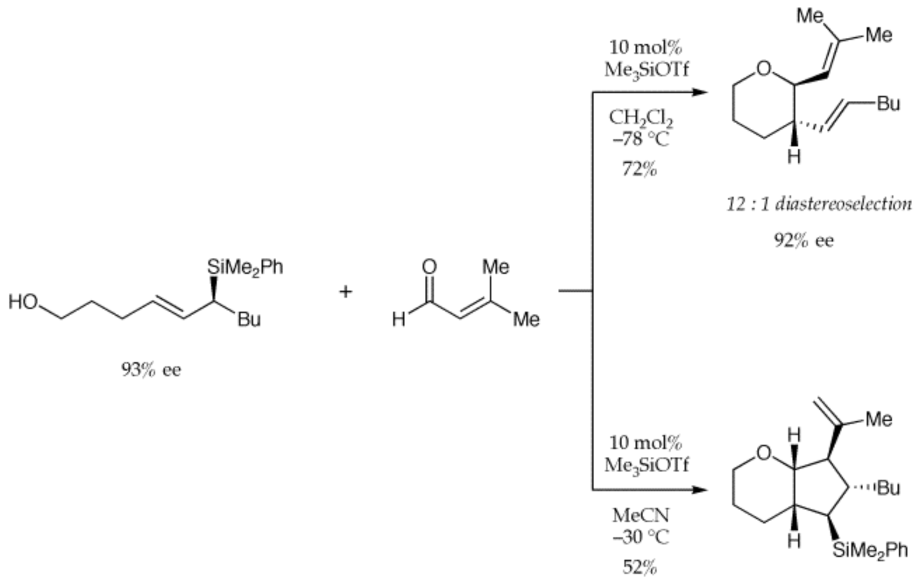
Provide a mechanism for the following transformation (O. R. Rodig, *J. Org. Chem.* **1971**, *36*, 2324).



**Problem 296**

Contributer: **Keith Woerpel**
Citation: *J. Org. Chem.* **1998**, *63*, 6096
Keywords: Rearrangement

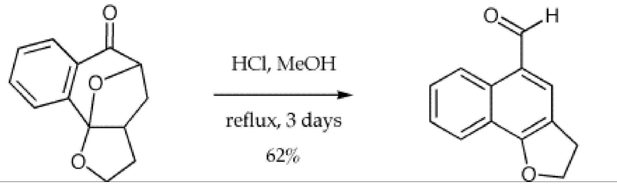
Provide a mechanism for the following transformations (Y. Ito, *J. Org. Chem.* **1998**, *63*, 6096). Your answers should account for the stereochemistry of the reactions. This paper shows several other examples of the top reaction.



## Problem 298

Contributer: **Keith Woerpel**
Citation: *J. Am. Chem. Soc.* **1988**, *110*, 2894
Keywords: Rearrangement

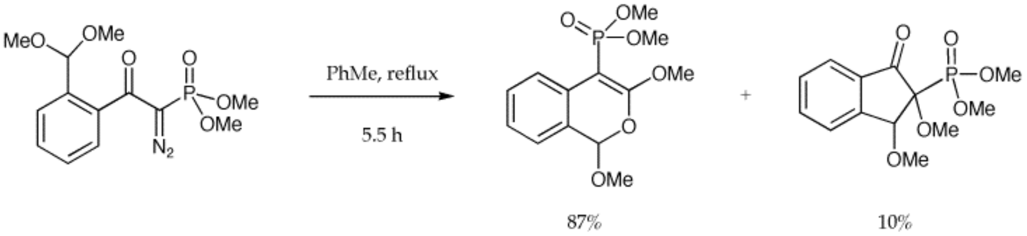
Provide a mechanism for the following transformation (A. Padwa *J. Am. Chem. Soc.* **1988**, *110*, 2894).



## Problem 299

Contributer: **Keith Woerpel**
Citation: *Tetrahedron* **1998**, *54*, 6457
Keywords: Rearrangement

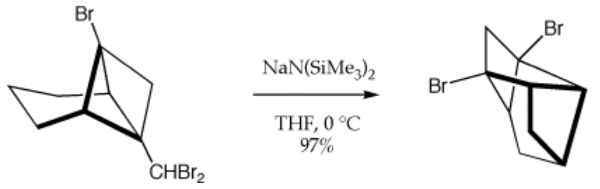
Thermal decomposition of functionalized diazo compounds was found to provide some interesting structures (F. Léost, *Tetrahedron* **1998**, *54*, 6457). This paper includes several examples. Provide mechanisms for the formation of the following two products.



## Problem 304

Contributer: **Keith Woerpel**
Citation: *J. Am. Chem. Soc.* **1999**, *121*, 7476
Keywords: Rearrangement

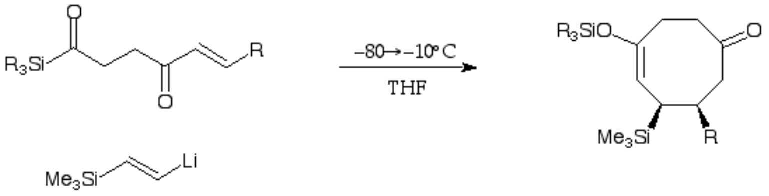
Provide a mechanism for the following transformation (G. Szeimies, *J. Am. Chem. Soc.* **1999**, *121*, 7476).



## Problem 305

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2003**, ASAP
Keywords: Rearrangement

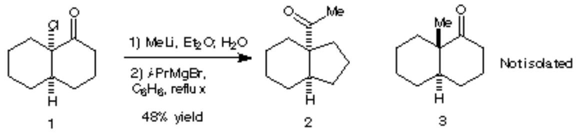
A newly developed strategy has recently been reported for the construction of eight-membered rings (*Org. Lett.* **2003**, ASAP). Provide a plausible mechanism for the illustrated transformation. Please include conformational drawings that also explain the stereochemical outcome of the transformation.



## Problem 310

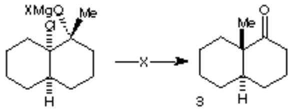
Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1972**, *37*, 4090
Keywords: Rearrangement

Sisti and Citale (*J. Org. Chem.* 1972, *37*, 4090) have reported that cis chlorodecalone (1) was treated with methyllithium and a mixture of stereoisomeric alcohols was isolated. When this mixture of alcohols was converted to the derived magnesium alkoxides and heated in benzene, the ring contracted product (2) was isolated in 48% overall yield. It is interesting that none of the trans methyldecalone (3) was observed.



Part A. Rationalize the formation of 2 from both diastereomeric alcohols derived from 1. Please use carefully rendered three dimensional drawings to illustrate your answer.

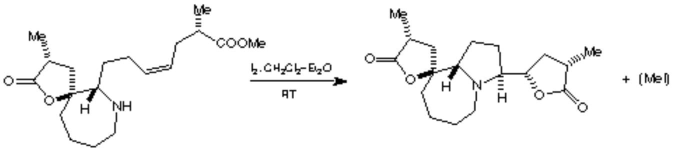
Part B. Explain why the indicated alkoxide does not lead to the formation of 3.



## Problem 311

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1986**, *111*, 1923
Keywords: Rearrangement

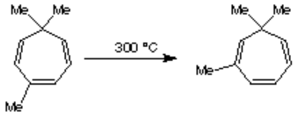
The iodine-induced transformation shown below is a key step in the Williams synthesis of croomine (*JACS* 1989, *111*, 1923). Given the stereochemical outcome of the illustrated transformation, propose a detailed mechanism for this reaction sequence. Williams has recently provided another closely reaction of the same design (*Org. Lett* 2003, *5*, 3361).



## Problem 315

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1966**, *88*, 2494
Keywords: Rearrangement

Berson and co-workers have studied the thermal isomerization illustrated below (*JACS* 1966, *88*, 2494-2502).

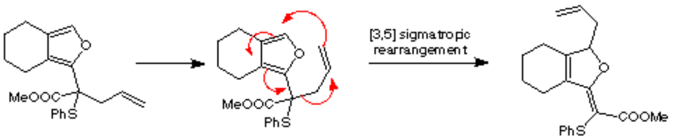


Provide a rationalization of these results. Three-dimensional drawings are recommended.

## Problem 325

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2003**, *5*, 2619
Keywords: Rearrangement

The furan shown below rearranges on standing at room temperature to the product shown below (*Org. Lett* 2003, *5*, 2619). The mechanism proposed in the article for this transformation is a [3,5] sigmatropic rearrangement.



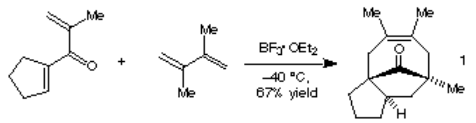
Part A. Please provide a Dewar-Zimmerman and an FMO analysis that illustrates why this is not a plausible mechanism.

Part B. Please provide a mechanism for this rearrangement that is more consistent with the rules of orbital symmetry. You do not need to provide a justification for the step(s) of your mechanism.

## Problem 326

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2003**, *5*, 2747-2750
Keywords: Rearrangement

The illustrated transformation reported this year by West and co-workers (*Org. Lett.* 2003, *5*, 2747-2750) rapidly facilitates the construction of the complex tricyclic ketone 1 in 67% yield.

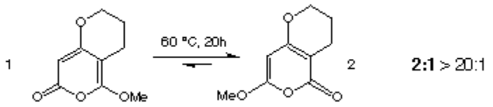


Please provide a concise mechanism for this transformation. Use 3-dimensional representations where appropriate to illustrate your answer.

## Problem 327

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1989**, *30*, 3509-3512
Keywords: Rearrangement

In 1989, Cha reported a study on the thermal isomerization of alkoxypyrones (*Tet. Lett.* 1989, *30*, 3509-3512). One of the cases studies was the rearrangement of 1→2.



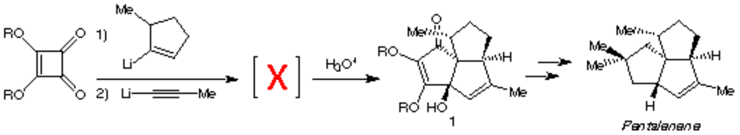
Part A. Provide a mechanism for this rearrangement in the space below.

Part B. At equilibrium, 2 is strongly favored over 1 (2:1 >20:1). Please rationalize product stability on the basis of the anomeric effect as was done by the authors.

## Problem 328

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2002**, *4*, 4547-4549
Keywords: Rearrangement

A synthesis of the hydrocarbon pentalenene was recently disclosed by Paquette and co-workers (*Org. Lett.* 2002, *4*, 4547-4549). The pivotal reaction cascade that affords the pentalenene core 1 is illustrated below.

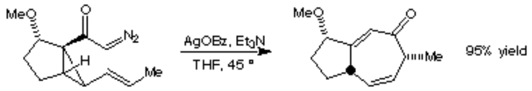


Please provide a mechanism for the reaction cascade that results in the production of the tricyclic core 1. Your answer should include clear 3-D drawings where relevant and should clearly identify intermediate X.

## Problem 332

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2003**, *125*, 13624-13625
Keywords: Rearrangement

Stoltz and co-workers recently reported the interesting rearrangement illustrated below (*JACS* 2003, *125*, 13624).

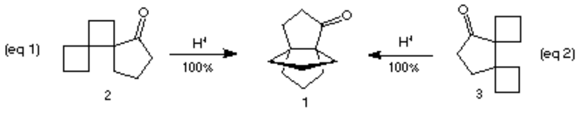


Please provide a mechanism for the illustrated transformation. Your answer should include clear 3-D drawings where relevant and should provide the stereochemistry of the major product diastereoisomer.

## Problem 335

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1985**, *26*, 5277-5280
Keywords: Rearrangement

Fitjer and co-workers (*Tet. Lett.* 1988, *29*, 263) have reported a very interesting approach to the [3,3,3]propellane 1. This tricyclic ketone may be produced in quantitative yield through acid-catalyzed rearrangement of ketones 2 or 3.

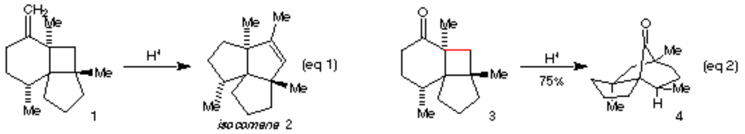


Please provide a plausible mechanism for the rearrangement 2→1 (eq 1). Use 3-dimensional representations where appropriate to illustrate your answer.

## Problem 336

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1982**, *103*, 82-87
Keywords: Rearrangement

We have discussed the Pirrung approach to the synthesis of isocomene (2) (*JACS* 1982, *103*, 82-87) that features the acid catalyzed rearrangement illustrated below (eq 1). In the Pirrung study the rearrangement of ketone 3 was also reported (eq 2).

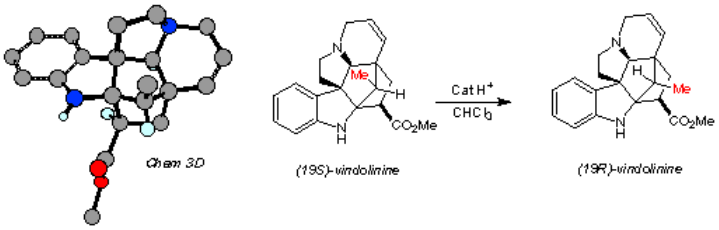


Please provide a plausible mechanism for the rearrangement 3→4 (eq 2). Use 3-dimensional representations where appropriate to illustrate your answer.

## Problem 338

Contributer: **David A. Evans**
Citation: *Z. Naturforsch* **1986**, 386
Keywords: Rearrangement

The indole alkaloid *(19S)*-vindolinine readily isomerizes into its (*19R*) diastereomer under the influence of trace amounts of acid present in chloroform (Atta-ur-Rahman Z. *Naturforsch* 1986, 386).

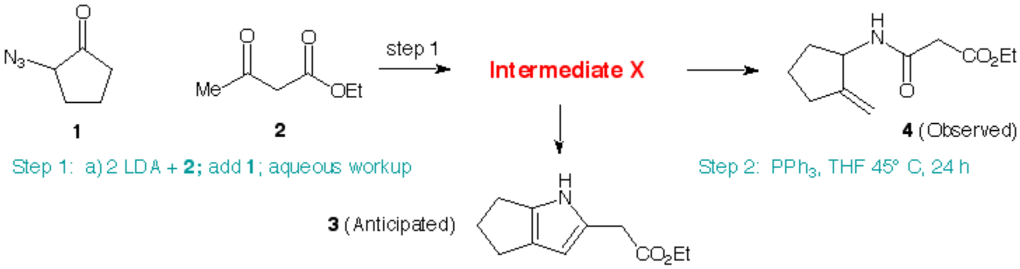


Provide a mechanism for this rearrangement in the space below. Explain why (19R) isomer is more stable than (19S).

## Problem 343

Contributer: **David A. Evans**
Citation: *Chem. Commun.* **2003**, 3044
Keywords: Rearrangement

Langer and co-workers recently reported the interesting *errant* Staudinger reaction illustrated below (*Chem Comm.* **2003**, 3044). The anticipated reaction product was pyrrole **3** while the observed product was **4**.

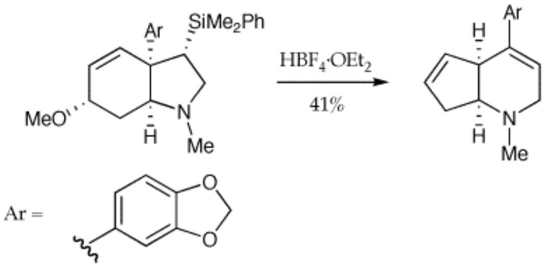


Provide a detailed mechanism for this transformation.

## Problem 344

Contributer: **Keith Woerpel**
Citation: *J. Org. Chem.* **1994**, *59*, 5662
Keywords: Rearrangement

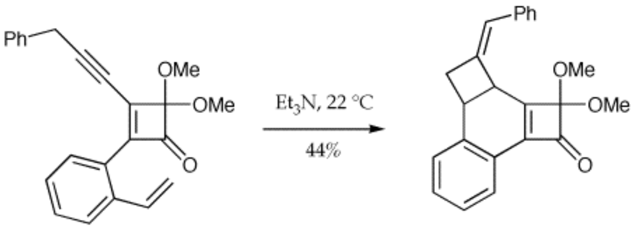
As part of a planned synthesis of an *Amaryllidaceae* alkaloid, Pearson and Postich attempted a Tamao-Fleming oxidation, but a rearranged product was obtained. Provide a mechanism for the following transformation (W. H. Pearson, M. J. Postich, *J. Org. Chem.* **1994**, *59*, 5662).



## Problem 346

Contributer: **Keith Woerpel**
Citation: *J. Org. Chem.* **2002**, *67*, 1388
Keywords: Rearrangement

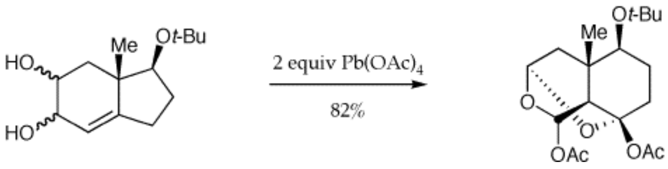
Provide a mechanism for the following transformation (A. R. Hergueta, H. W. Moore, *J. Org. Chem.* **2002**, *67*, 1388).



## Problem 347

Contributer: **Keith Woerpel**
Citation: *J. Org. Chem.* **2002**, *67*, 2447
Keywords: Rearrangement

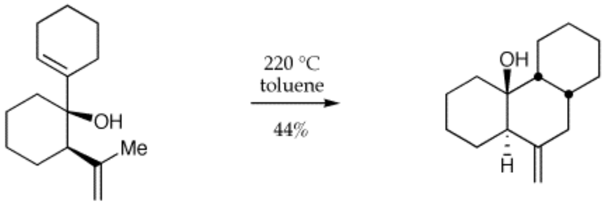
Provide a mechanism for the following transformation (C. Unaleroglu, V. Aviyente, S. Arseniyadis, *J. Org. Chem.* **2002**, *67*, 2447).



## Problem 349

Contributer: **Keith Woerpel**
Citation: *Organic Lett.* **2000**, *2*, 663
Keywords: Rearrangement

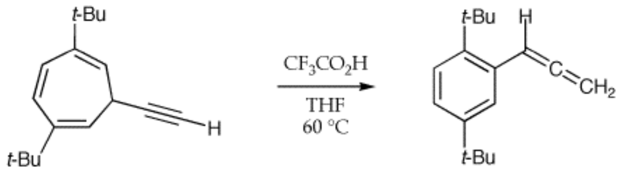
Thermolysis of 1,2-divinylcyclohexanols leads to some interesting products (J. M. Warrington, G. P. A. Yap, L. Barriault, *Org. Lett.* **2000**, *2*, 663). Provide a mechanism for this reaction, including a rationalization of stereochemistry.



## Problem 353

Contributer: **Keith Woerpel**
Citation: *Organic Lett.* **2000**, *2*, 3011
Keywords: Rearrangement

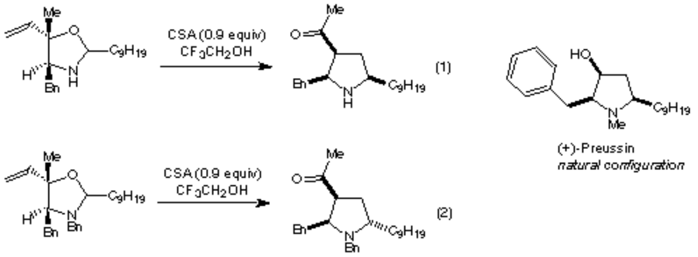
Provide a mechanism for the following reaction (T. Kitagawa, *Org. Lett.* **2000**, *2*, 3011).



## Problem 359

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.*
Keywords: Rearrangement

An elegant enantiodivergent synthesis of the potent anti-fungal reagent Preussin was reported by Overman (*JACS* 1994, 11241.).



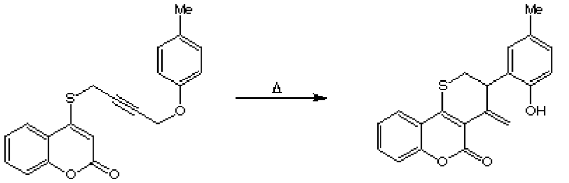
Part A. Provide a mechanism for the transformation illustrated in Eq 1. Where stereochemicasl issues are involved, 3-dimensional drawings should be employed.

Part B. Provide a mechanism for the transformation illustrated in Eq 2. Where stereochemicasl issues are involved, 3-dimensional drawings should be employed.

## Problem 364

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2002**, *4*, 2629
Keywords: Rearrangement

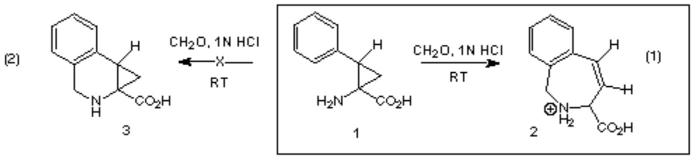
A recent paper by Majumdar and co-workers reported the transformation illustrated below (*Organic Lett* 2002, *4*, 2629). Please provide a mechanism for this process. Feel free to use trace quantities of HX when needed.



## Problem 365

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2001**, *66*, 2884
Keywords: Rearrangement

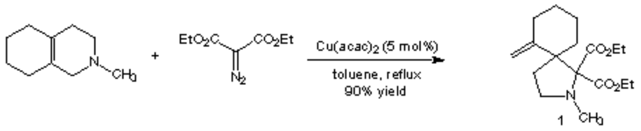
A recent paper by Martens (*JOC* 2001, *66*, 2884) reported the reaction shown below (Eq 1). Please provide a mechanism for the conversion of 1 to 2. It is noteworthy that the Pictet-Spengler of 1 does not give 3.



## Problem 367

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2003**, *5*, 4775
Keywords: Rearrangement

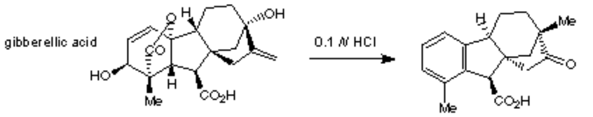
A recent paper by Workman and co-workers (*Org. Lett.* 2003, *5*, 4775) describe an efficient reaction for the formation of spiro-heterocycle 1. Propose a mechanism for the formation of 1.



## Problem 370

Contributer: **Jonathan scheerer**
Citation:
Keywords: Rearrangement

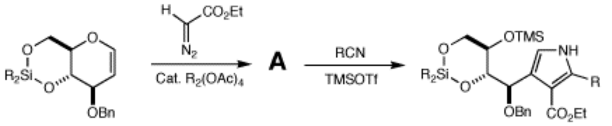
Gibberellic acid is a notoriously sensitive natural product. Rearrangement occurs readily in both acidic and basic conditions. Provide a mechanism for the illustrated rearrangement under dilute HCl.



## Problem 374

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2003**, *5*, 5099
Keywords: Rearrangement

Pagenkopf and Yu have recently reported a new "diversity-oriented" synthesis of pyrroles (*Org. Lett.* **2003**, *5*, 5099). The two-step process illustrated below will accomodate a range of "R" substituents.

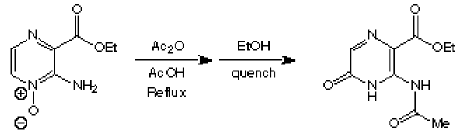


Provide a mechanism for the overall process and clearly identify intermediate **A**.

## Problem 376

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1975**, 2431
Keywords: Rearrangement

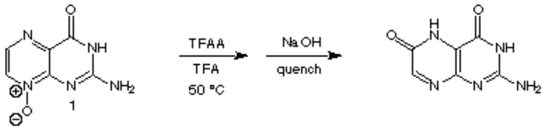
The Katada rearrangement is a method to effect site specific oxidation of certain aromatic heterocycles. Please provide a mechanism for the specific example of the Katada rearrangement shown below (*J. Org. Chem.* 1975, 2431).



## Problem 377

Contributer: **Travis Dunn**
Citation: *J. Org. Chem.* **1975**, 2431
Keywords: Rearrangement

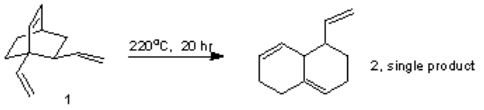
The Katada rearrangement is a method to effect site specific oxidation of certain aromatic heterocycles. Please provide a mechanism for the specific example of the Katada rearrangement shown below (*J. Org. Chem.* 1975, 2431). When heterocycle 1 was treated with warm trifluoroacetic anhydride and trifluoroacetic acid, the unexpected product 2 was isolated. Please provide a mechanism for this unusual rearrangement.



## Problem 378

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1994**, *116*, 1776
Keywords: Rearrangement

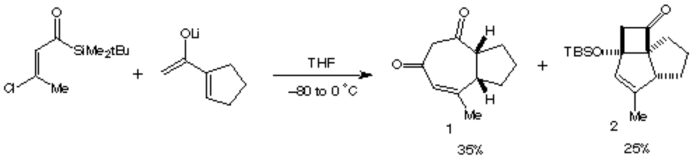
Paquette and co-workers have reported that thermal isomerization of 1 occurs to give triene 2 as a single diastereomer (*JACS* 1994, *116*, 1776). Provide a plausible mechanism for this transformation and provide the product stereochelmical relationship of 2 based on the absolute stereochlemistry of the starting triene 1.



## Problem 380

Contributer: **David A. Evans**
Citation: *Organic Lett.* **1999**, 677
Keywords: Rearrangement

Takeda and co-workers have developed an efficient strategy for the synthesis of fused 5,7 ring systems by reacting acylsilanes with lithium enolates (*Org. Lett.*,1999, 677). Although the 5,7 bicyclic product 1 is often observed, the nature of the enolate nucleophile can affect the course of the reaction.

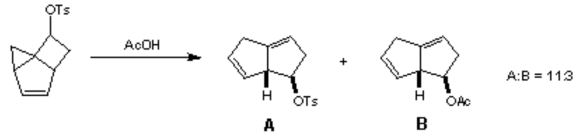


Provide a mechanism for the formation of both the anticipated 5,7 bicycle 1 and the tricyclic ketone 2.

## Problem 383

Contributer: **David A. Evans**
Citation: *Tetrahedron* **2000**, *56*, 2591
Keywords: Rearrangement

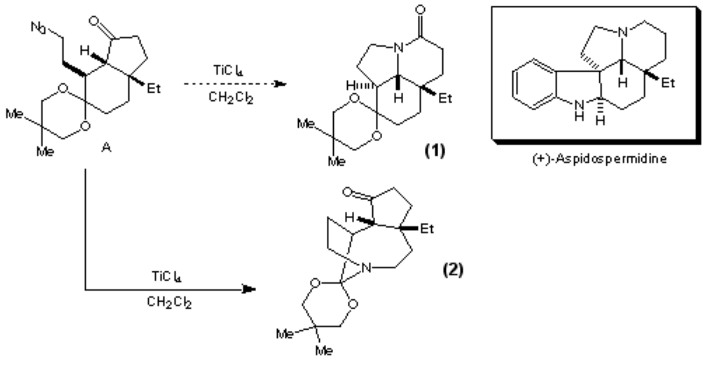
Kass has reported the interesting carbonium ion rearrangement shown below (*Tetrahedron*, 2000, *56*, 2591). Provide a mechanism for this transformation.



## Problem 384

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2000**, 1625
Keywords: Rearrangement

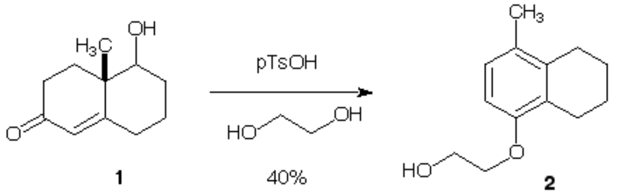
A key step in Aube's total synthesis of (+)-Aspidospermidine (*Org. Lett.*, 2000, 1625) involved the rearrangement shown in equation (1) to form the requisite nitrogen heterocycle. However, upon subjection of the starting azide to Lewis acidic conditions, an unexpected rearrangement occurred as shown in equation (2). Provide a mechanism for the formation of both the expected and unexpected products.



## Problem 387

Contributer: **Karl Scheidt**
Citation: *Tetrahedron Lett.* **1965**, *21*, 2297
Keywords: Rearrangement

The formation of ketals from ketones is usually a straightforward operation. However, it was found that treatment of unsaturated ketone **1** with pTsOH and ethylene glycol did not provide the expected ketal, but the aromatic compound **2** as the major product (Tetrahedron Lett. **1965**, *21*, 2297).

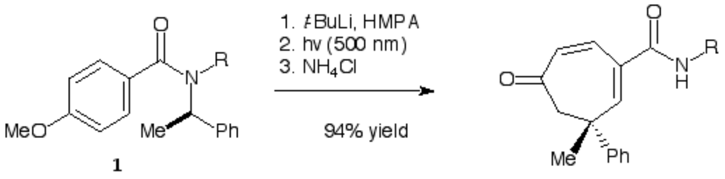


Provide a plausible mechanism for this reaction.

## Problem 391

Contributer: **Karl Scheidt**
Citation: *J. Am. Chem. Soc.* **2003**, *125*, 9278
Keywords: Rearrangement

A recent approach to the construction of 7-membered rings from aromatic systems such as **1** involves the following sequence of reactions (J. P. Clayden; F. E. Knowles & C. J. Menet *J. Am. Chem. Soc.* **2003** *125*, 9278-9279).

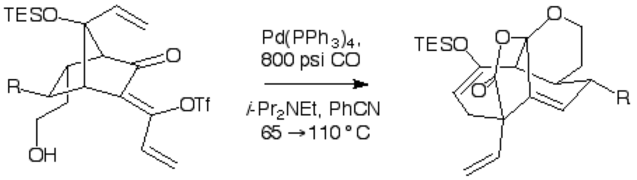


Propose a mechanism for this reaction and pay careful attention to any sigmatropic and pericyclic processess.

## Problem 404

Contributer: **Phillip S. Baran**
Citation: *Organic Lett.* **2000**, *2*, 2905
Keywords: Rearrangement

Leighton and Bio have recently disclosed the following approach to the core of CP-263,114 ( *Org. Lett* **2000**, 2905).

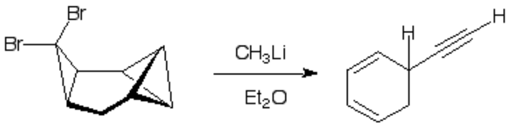


Please provide a mechanism for this transformation.

## Problem 405

Contributer: **Phillip S. Baran**
Citation: *Angew. Chem.* **1975**, 765
Keywords: Rearrangement

Lechner and Christl described this interesting, albeit unintended degradation of **1** upon treatment with methyllithium (*Angew. Chem. Int. Ed.* **1975**, 765). These studies were undertaken en route to tetrahedrane, although the ultimate goal was never realized.

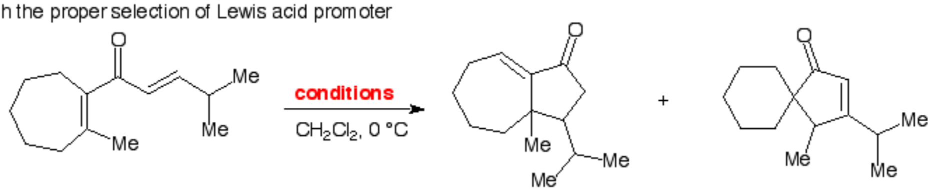


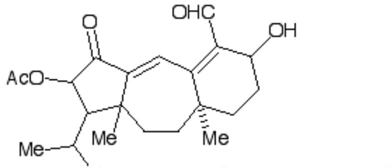
Please provide a mechanism for this transformation.

## Problem 407

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2004**, *6*, 613
Keywords: Rearrangement

Chiu and Li have reported the illustrated acid-promoted cyclization that was designed to serve as a pivotal bond construction in the synthesis of guanacastepene A (*Org. Lett* **2004**, *6*, 613). The authors note that the principal products may be regulated through the proper selection of Lewis acid promoter





*Guanacastepene A*

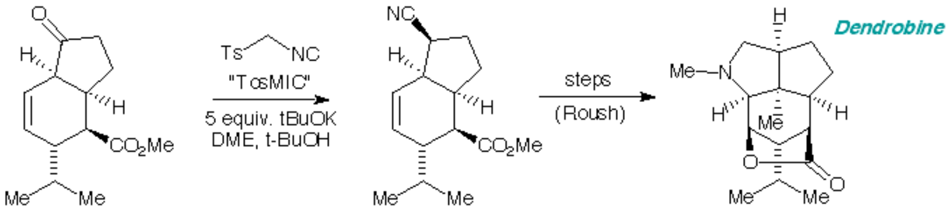
| conditions | ratio | yield |
|---|---|---|
| $BF_3 \cdot OEt_2$ | >95:05 | 98% |
| $BCl_3$ | 05:95 | 92% |

Provide a detailed mechanism for the formation of both products. Please denote the anticipated relative stereochemical relationship for the hydroazulane product.

## Problem 409

Contributer: **Dan O,Malley**
Citation: *J. Org. Chem.* **1977**, *42*, 3114
Keywords: Rearrangement

Tosylmethyl isocyanate (TosMIC) is a remarkable reagent developed by van Leusen and co-lworkers at the University of Groningen. One use of this reagent is for the one-carbon homologation of ketones to nitriles as illustrated below (*J. Org. Chem.* **1977**, *19*, 3114). In the illustrated application, Roush has applied this methodolgy to his synthesis of dendrobine (*J. Am. Chem. Soc.* **1980**, *4*, 1390).

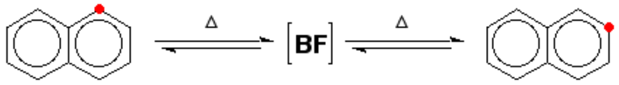


Provide one or more plausible mechanisms for this transformation.

## Problem 410

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1991**, *113*, 9692
Keywords: Rearrangement

In 1977 L. T. Scott reported the remarkable automerization of naphthalene shown below (*JACS* **1977**, *99*, 4560). This study was followed up with a second report that provided aditional evidence that suggested that an intermediate, **BF**, is formed during the course of this rearrangement (*JACS* **1991**, *113*, 9692).



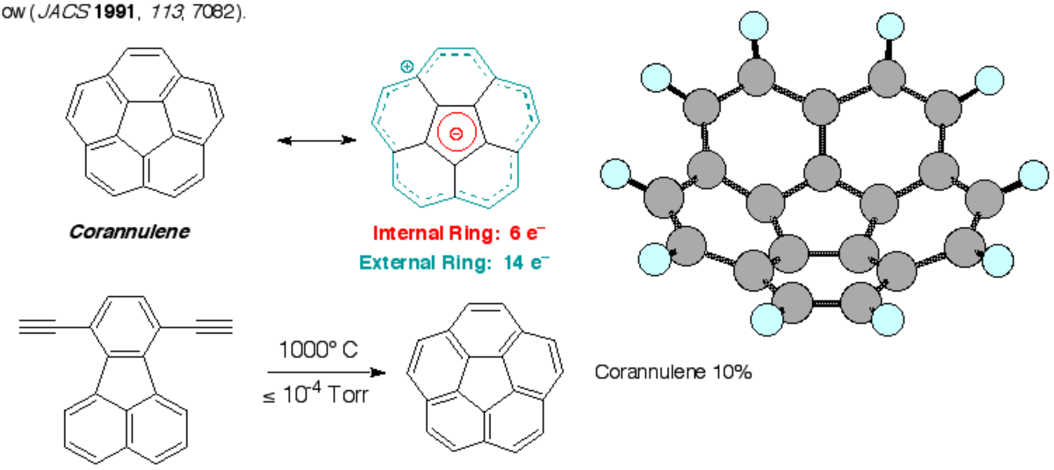
α–$^{13}$C-labeled $C_{10}H_8$ is isomerized into β–$^{13}$C-labeled $C_{10}H_8$ at 1035 °C

Provide one or more plausible mechanisms for this transformation and propose a reasonable structure for intermediate **BF**.

## Problem 411

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1991**, *113*, 7082
Keywords: Rearrangement

Corranulene, the bowl-shaped aromatic hydrocarbon illustrated below, is an aromatic hydrocarbon of theoretical interest. The interest in this structure follows from its polarized resonance structure that generates two internal Huckel 6– and 14–pi electron systems. the first synthesis of corranulene was reported by Lawton in 1966 through a multistep synthesis sequence (*JACS* **1966**, *88*, 380). Subsequently, L. T. Scott reported the elegant high temperature synthesis of corannulene illustrated below (*JACS* **1991**, *113*, 7082).

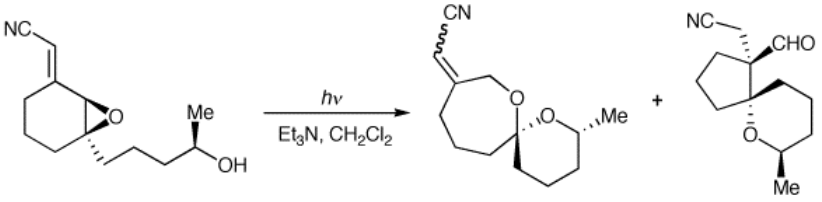


Provide one or more plausible mechanisms for this transformation.

## Problem 414

Contributer: **Ryan Shenvi**
Citation: *Chem. Pharm. Bull. Japan* **1995**, *10*, 1621
Keywords: Rearrangement

Ishii and co-workers (*Chem. Pharm. Bull.* **1995**, *10*, 1621) reported photochemical reactions of several α,β–unsaturated γ,δ–epoxy nitriles, one of which is shown below.

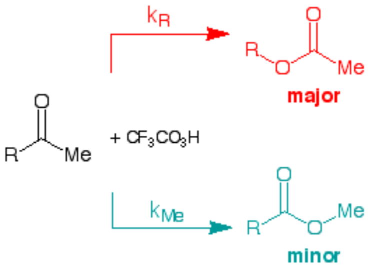


Provide a detailed mechanism for this reaction, accounting for stereochemistry when possible.

## Problem 416

Contributer: **David A. Evans**
Citation: *Angew. Chem.* **2000**, *39*, 2852
Keywords: Rearrangement

An example of a generic Baeyer-Villiger reaction is illustrated below. Precedent has established that oxygen insertion occurs preferentially between the carbonyl and the more sterically demanding C=O substituent (R). A representative set of data is provided below.



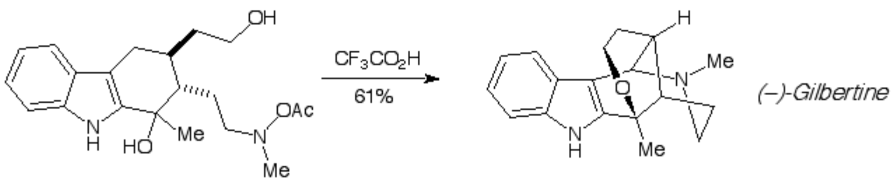
| R | $k_R / K_{Me}$ |
|---|---|
| $CH_3CH_2$ | 72 |
| $CH_3(CH_2)_2$ | 150 |
| $(CH_3)_3C$ | 830 |
| $PhCH_2$ | >2000 |

Provide a rationalization for this transformation using three-dimensional drawings. Do not ignore the important stereoelectronic issues associated with this transformation. Accordingly, begin by identifying the important HOMO-LUMO interactions.

## Problem 417

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2004**, *126*, 3634-3638
Keywords: Rearrangement

An elegant synthesis of (–)-gilbertine has been recently reported by Jireck and Blechert (*JACS* **2004**, *126*, 3534-3538). The pivotal transformation in this synthesis is illustrated below:

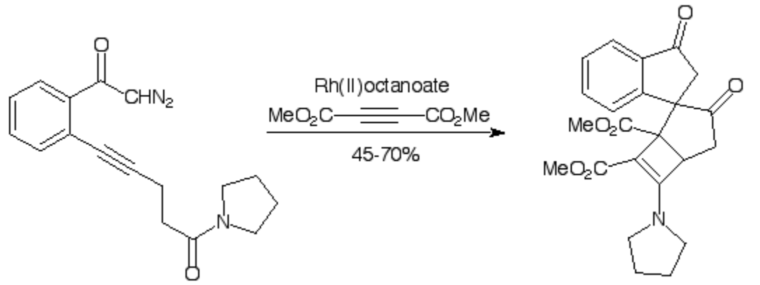


Provide a plausible mechanism for this transformation.

## Problem 419

Contributer: **Dan O'Malley**
Citation: *Tetrahedron Lett.* **1993**, *49*, 7853
Keywords: Rearrangement

While investigating the reactivity of α-diazoketones, Padwa and co-workers (*Tetrahedron Lett.* **1993**, *49*, 7853) discovered the interesting reaction of diazoketone **1** under the conditions shown below:



**1**

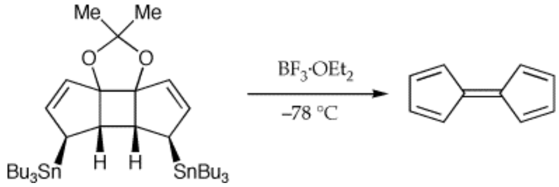
**2** 1:1 mixture of diastereomers

Provide a detailed mechanism for the formation of spirocycle **2**.

## Problem 420

Contributer: **Keith Woerpel**
Citation: *J. Org. Chem.* **2004**, *69*, 2516
Keywords: Rearrangement

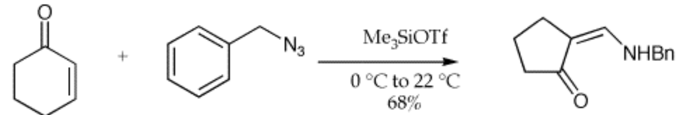
In the course of their studies of unusual hydrocarbons, Myers and co-workers carried out the following transformation (*J. Org. Chem.* **2004**, *69*, 2516). Provide a mechanism.



## Problem 421

Contributer: **Keith Woerpel**
Citation: *Organic Lett.* **2003**, *5*, 3899
Keywords: Rearrangement

Aubé and co-workers studied the reactions of azides with α,β-unsaturated carbonyl compounds, and they observed some interesting products (*Org. Lett.* **2003**, *5*, 3899). Provide a mechanism for the following transformation.

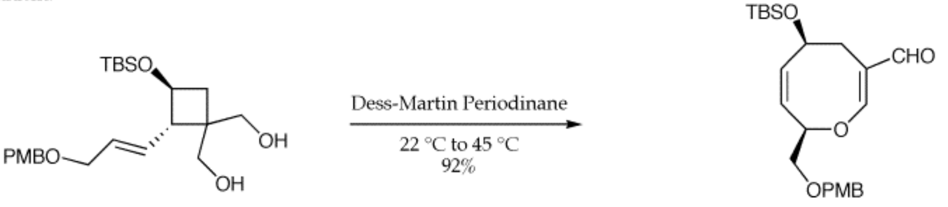


3 : 2 = *Z* : *E*

## Problem 422

Contributer: **Keith Woerpel**
Citation: *Organic Lett.* **2002**, *4*, 3891
Keywords: Rearrangement

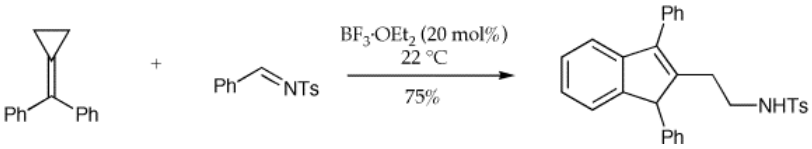
The following transformation is a key step in Boeckman's synthesis of laurenyne (*Org. Lett.* **2002**, *4*, 3891). Provide a mechanism.



## Problem 428

Contributer: **Keith Woerpel**
Citation: *Organic Lett.* **2004**, *6*, 1175
Keywords: Rearrangement

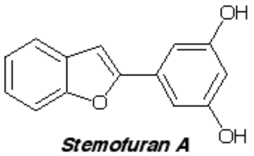
A number of interesting transformations utilizing alkylidene cyclopropanes were recently reported (M. Shi *Org. Lett.* **2004**, *6*, 1175). Provide a mechanism for the following example.



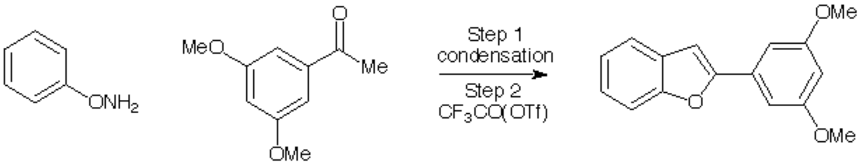
## Problem 432

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2004**, *6*, 1761
Keywords: Rearrangement

Benzofurans are widespread heterocycles in nature and are common subunits in a range of biologically active compounds. An example of a benzofuran having antifungal and insecticidal activities is stemofuran A. An approach to the synthesis of this hetercycle has recently been reported by Naito (*Org. Lett.* **2004**, *6*, 1761). The outline of the synthesis is illustrated below. The reagent employed in Step 2 is trifluoroacetyl triflate, a strong acylating agent. Provide a plausible mechanism for this transformation.



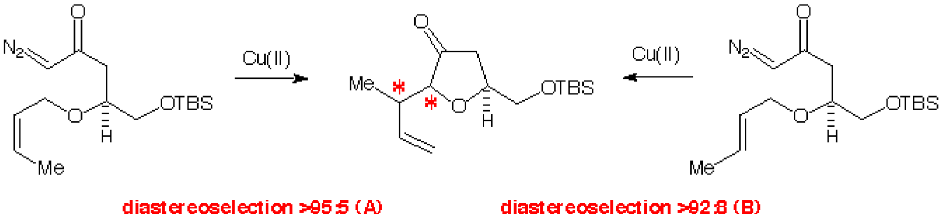
***Stemofuran A***



## Problem 433

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2004**, *6*, 1773
Keywords: Rearrangement

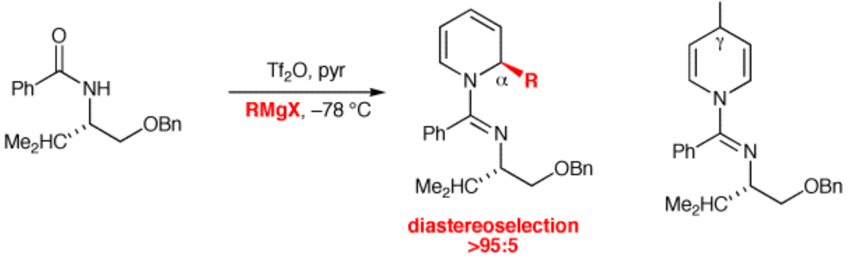
Clark and co-workers recently reported the highly stereoselective transformation of the (Z) and (E) crotyl ethers illustrated below (*Org. Lett.* **2004**, *6*, 1773–1776). As the authors note, the the literature precedents for the preferred geometry (**exo** versis **endo**) are not in universal agreement. Draw out the intermediates and transition states for the rearrangement of the (Z) crotyl ether leading to the two princpal product diastereomers. Speculate what transition state control elements might be operative to favor one of the two transition states and draw the two principal product diatereomers **A** and **B**.



## Problem 434

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2001**, *123*, 11829
Keywords: Rearrangement

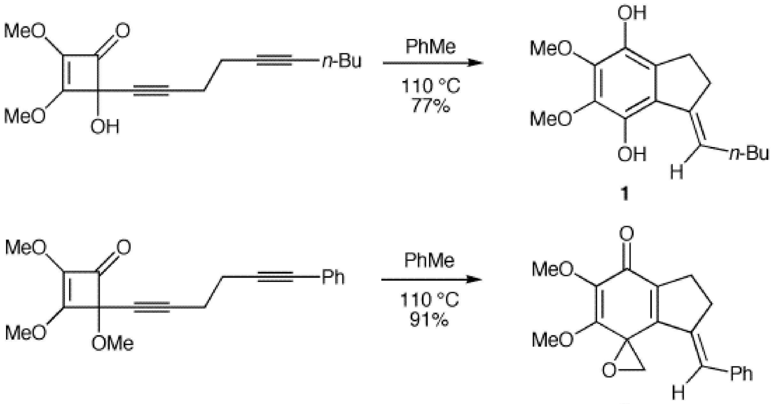
Charette and co-workers recently reported a creative approach to the enantioselective synthesis α-substituted piperidine derivatives illustrated below (*JACS* **2001,** *123,* 11830). The alpha regioselectivities are generally >10:1 while the alpha diastereoselections are reported to be >95:5. Provide a detailed mechanism for the overall transformation. Provide a rationalization for the stereochemical outcome of the addition reaction. Three-dimensional drawings that illustrate chirality transfer should be provided.



## Problem 435

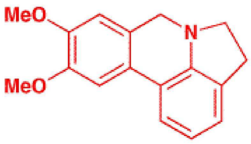
Contributer: **Mihael DeMartino**
Citation: *J. Org. Chem.* **1996**, *61*, 9169
Keywords: Rearrangement

While engaged in research involving cyclobutanones, Xia and Moore discovered the following two transformations (*J. Org. Chem.* **1992**, *57*, 3765). Four years later, the first of these discoveries was employed in the total synthesis of the assoanine, **3** (*J. Org. Chem.* **1996**, *61*, 9168), a biologically interesting pyrrolophenanthride alkaloid isolated from *Amaryllidaceae* .



**1**

**2**



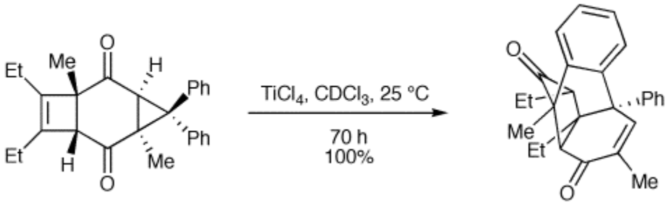
***Assoanine,* 3**

Provide plausible mechanisms for these transformations.

## Problem 438

Contributer: **Ryan Shenvi**
Citation: *J. Org. Chem.* **2004**, *42*, 4577
Keywords: Rearrangement

Oshima and co-workers reported the Lewis-acid catalyzed transformation of strained tricyclo[5.2.0.0]non-8-ene-2,6-diones to give, in most cases, a mixture of products (*Tetrahedron Lett.*, **2001**,*42*, 5025). In one case, however, the reaction was both quantitative and stereoselective (*J. Org. Chem.*, **2004**, *69*, 4577), yielding the quadracycle shown below.

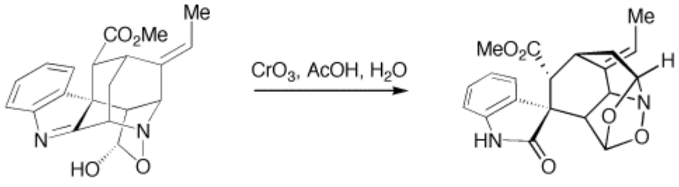


Provide a mechanism for this transformation.

## Problem 439

Contributer: **Carlos Guerrero**
Citation: *Helv. Chem. Acta* **1977**, *60*, 1419
Keywords: Rearrangement

While studying alkaloids isolated from *Alstonia scholaris* (Helv. Chim Acta **1977**, *60*, 1419), Schmid *et al.* discovered the hitherto-unknown indole alkaloid nareline (**1**). Oxidation ($CrO_3$, AcOH) gave structure **2**, termed "oxonareline." Provide a plausible mechanism for this conversion.



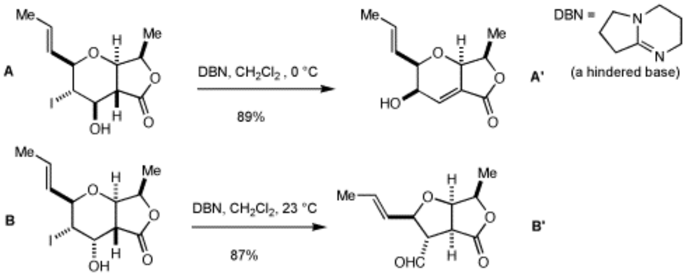
**1**: nareline **2**: oxonareline

Provide a plausible mechanism for this conversion.

## Problem 498

Contributer: **Pavel Nagorney**
Citation: *J. Org. Chem.* **2004**, 5517
Keywords: Rearrangement

Products from the iodoetherification (**A** and **B**), when exposed to base (DBN), undergo different rearrangements. Please provide mechanisms that account for the divergent reaction pathways.

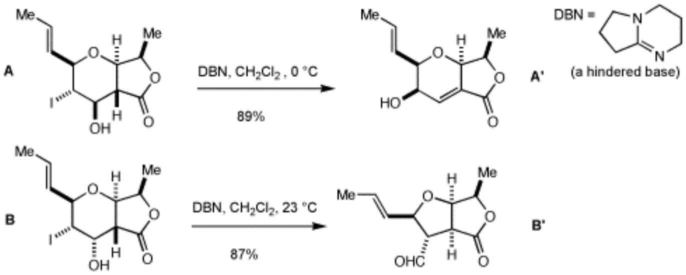


This problem is related to Problem 497

## Problem 499

Contributer: **Jon Scheerer**
Citation: *J. Org. Chem.* **2004**, 5517
Keywords: Rearrangement

Products from the iodoetherification (**A** and **B**), when exposed to base (DBN), undergo different rearrangements. Please provide mechanisms that account for the divergent reaction pathways.

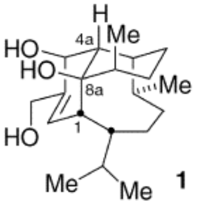


This problem is related to Problem 497

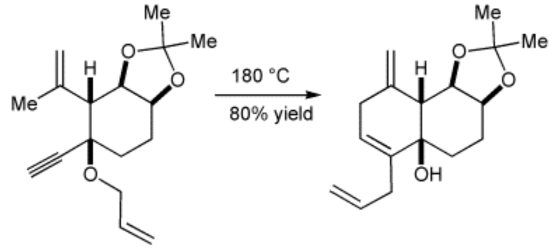
## Problem 596

Contributer: **Louis Morency**
Citation: *Tetrahedron Lett.* **2004**, *45*, 6105
Keywords: Rearrangement

In a recent paper by Morency and Barriault (*Tet. Lett.* **2004**, *45*, 6105), the following transformation was reported. The series of thermally induced rearrangements afforded the cis decalin product as a single diastereoisomer in 80% yield. This transformation was reported as a model study for eventual application to the synthesis of vinigrol (**1**). Provide a plausible mechanism for this transformation and explain the selectivity



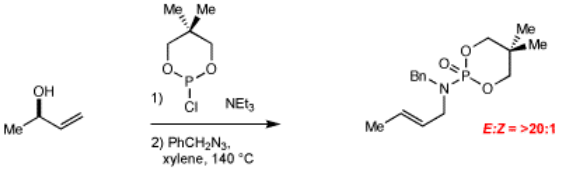
**1**



## Problem 633

Contributer: **Jon Scheerer**
Citation: *J. Am. Chem. Soc.* **2004**, *126*, 5364
Keywords: Rearrangement

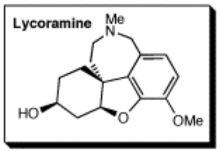
Mapp and co-workers disclosed a unique synthesis of allylic amines (*JACS*, **2004**, *126*, 5364.). Please provide a mechanism for the process that accounts for the observed the olefin selectivity.

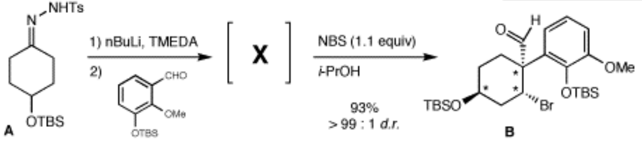


## Problem 698

Contributer: **Jon Scheerer**
Citation: *Organic Lett.* **2004**, *63*, 4691
Keywords: Rearrangement

A synthesis of lycoramine was recently published (Tu, *Org. Lett.* **2004**, *6*, 4691.). A sequence from the report is provided below. Please provide a mechanism for the overall transformation (**A** to **B**) that explains the high diastereoselectivity of the process. Your answer should highlight intermediate **X**.

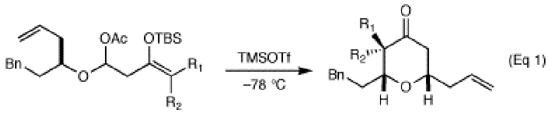




## Problem 699

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2004**, *126*, 15652
Keywords: Rearrangement

Rychnovsky and Dalgard (*JACS* **2004**, *126*, 15652) have reported the new diastereoselective pyranone synthesis illustrated below (Eq 1).

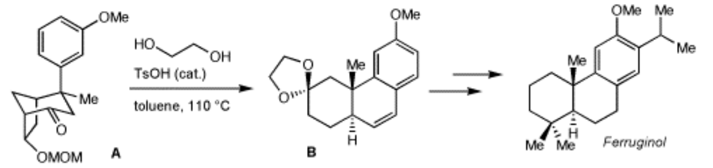


Please provide a mechanism for this rearrangement that accounts for the stereochemical outcome. Three-dimensonal representations are required for your rationalization the steps involving chirality transfer.

## Problem 701

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2001**, *36*, 1737
Keywords: Rearrangement

Ogasawara and co-workers have utilized the [3.2.1] bicyclic structure for the synthesis of a wide variety of terpene natural products. In the case at hand, [3.2.1] bicycle **A** was coverted to **B** in one operation (*Org. Lett.* **2001**, *3*, 1737) en route to (+)-ferruginol.

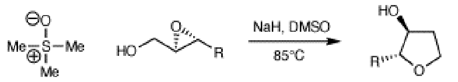


Please provide a mechanism for the conversion of **A** to **B**. Use 3-D pictures where relevant.

## Problem 714

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2004**, *126*, 13600
Keywords: Rearrangement

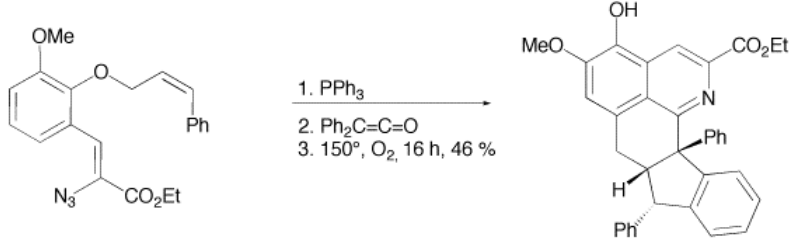
Provide a reasonable mechanism for the following reaction reported by Borhan (*JACS* **2004,** *126,* 13600).



## Problem 715

Contributer: **Noah Burns**
Citation: *J. Org. Chem.* **1991**, *56*, 4006
Keywords: Rearrangement

In 1991, Molina and coworkers reported the following domino reaction sequence (*J. Org. Chem.* **1991**, *56*, 4008). Editorially speaking, this transforrmation is ideal for a final examination on the evaluation of pericyclic processes!

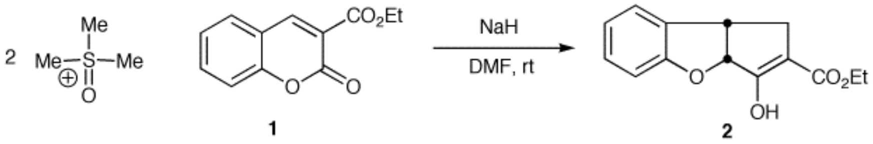


Provide a mechanism to account for this multisteptransformation.

## Problem 716

Contributer: **Michael DeMartino**
Citation: *Organic Lett.* **2001**, *3*, 1359
Keywords: Rearrangement

During the course of studying the regioselectivity of cyclopropanecarboxylate ring openings, Ohta and coworkers discovered the transformation illustrated below (*Tetrahedron Letters* **1995,** *36*, 5603). When coumarin **1** was treated with excess (2.4 eq) of the Corey-Chaykovsky ylide, an unexpected product **2** was generated in 64 %. This new reaction has been applied to the first total synthesis of (±)-linderol A (*Org. Lett.* **2001**, *3*, 1359).

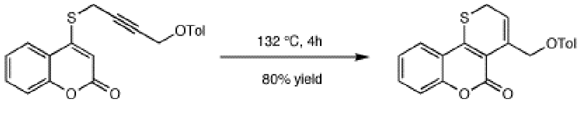


Provide a plausible mechanism for this transformation. The authors provide two different mechanisms (one in each of the aforementioned references), but did not attempt to prove either.

## Problem 727

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2002**, *45*, 2629
Keywords: Rearrangement

Please provide a mechanism for the following transformation (*Org. Lett.*, **2002**, 4, 2629.), being sure to classify any pericyclic processes that intervene.

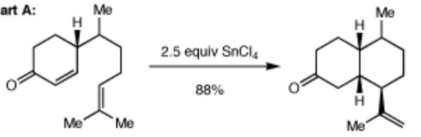


## Problem 728

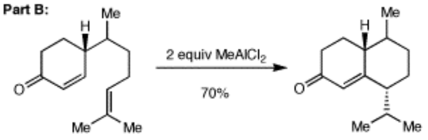
Contributer: **Jon Scheerer**
Citation: *Angew. Chem.* **2005**, *44*, 9926
Keywords: Rearrangement

A recent report has investigated the cationic cyclization of olefins under Lewis acidic conditions (*ACIE*, **2005**, *44*, 99.). The following examples (**A-C**) are of increasing difficulty and are framed in a specific order. Please provide a mechanism for each case illustrated.

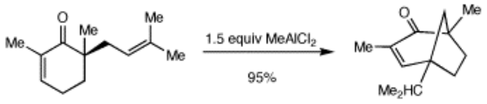
**Part A:**



**Part B:**



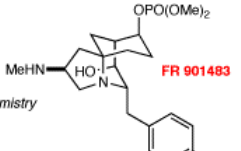
**Part B:** *For this question please provide 3-dimensional representations.*



## Problem 733

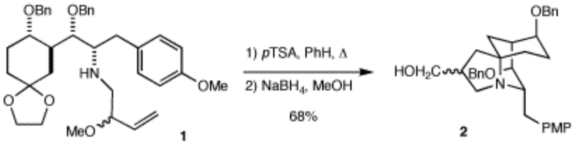
Contributer: **Jon Scheerer**
Citation: *J. Org. Chem.* **2004**, *ASAP*,
Keywords: Rearrangement

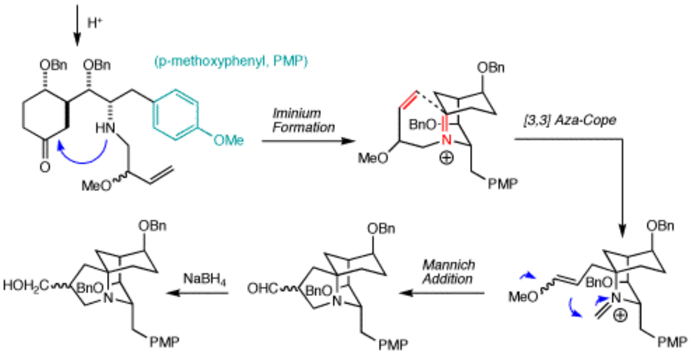
FR 901483 is an immunosuppressant developed by Fujisawa Pharmaceutical Company. Recently, a formal total syntheses of FR 901483 was disclosed that utilizes the transformation illustrated below (Brummond and Hong, *JOC*, **2004**, *ASAP*).



FR 901483

*Provide a mechanism for the conversion of **1** into **2** that explains the stereochemistry of the product. Utilize 3-D illustrations where necessary.*

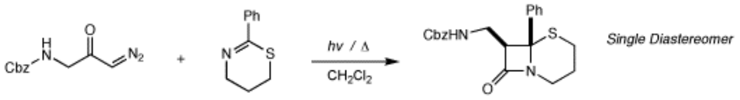




## Problem 735

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2005**, *70*, 334-337
Keywords: Rearrangement

α-Diazoketones are known to decompose to carbenes under photochemical excitation. It has recently been shown that in the presence of imines, the photo-decomposition of diazoketones provides β-lactams with good diastereocontrol (*JOC*, **2005**, *70*, 334-337).

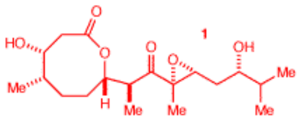


*Provide a mechanism for the above transformation. Your answer should include an explanation for the diastereoselectivity of this process.*

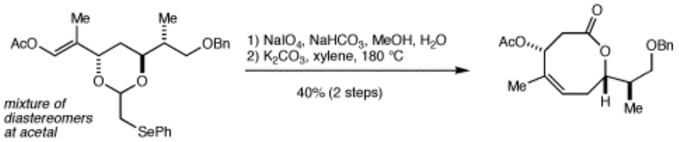
## Problem 738

Contributer: **Jon Scheerer**
Citation: *J. Am. Chem. Soc.* **2004**, *126*, 2194
Keywords: Rearrangement

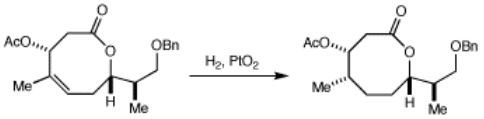
In 1991, Fenical and Clardy reported the isolation of eight-membered lactones, which were termed octalactins. The parent member, octalactin A (**1**), was recently synthesized by Holmes and co-workers (*JACS*, **2004**, *126*, 2194.).



**Part A.** Please provide a mechanism for the two-step sequence below that provides the eight-membered ring. Use 3-D illustrations in your explaination. *(NaIO$_4$ is only an oxidant)*



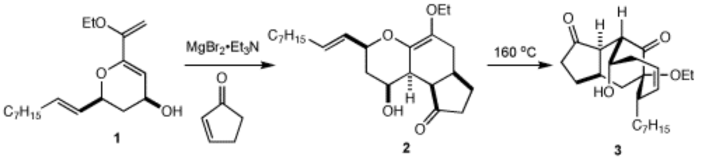
**Part B.** Please provide a rationale for the selective hydrogenation illustrated below.



## Problem 739

Contributer: **Jon Scheerer**
Citation: *Organic Lett.* **2004**, *67*, 1317
Keywords: Rearrangement

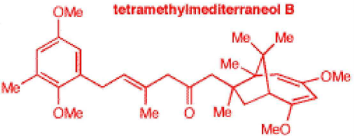
The rapid assembly of the bicyclo[5.3.1]undecane core of penostatin F was recently reported by Barriault and coworkers (*Org. Lett.* **2004**, *6*, 1317). In this remarkable transformation dihydropyran **1** is converted to the highly complex tricycle **3** in only two operations. Please provide a detailed mechanism for this reaction sequence. Be sure to indicate all pericyclic reactions.

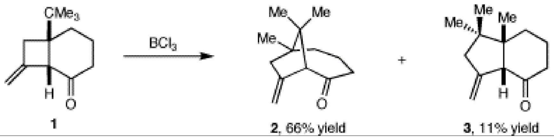


## Problem 740

Contributer: **Jon Scheerer**
Citation: *J. Org. Chem.* **1995**, *60*, 3318
Keywords: Rearrangement

The synthesis of racemic tetramethylmediterraneol B was reported by workers in Japan (*J. Org. Chem.* **1995**, 60, 3318-33). The pivotal step was the rearrangement of compound **1** into the [4.2.1] bicycle **2**, as found in the natural product. Provide a mechanism for the formation of **2** and **3**.

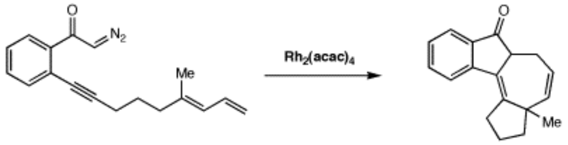




## Problem 741

Contributer: **Jon Scheerer**
Citation: *J. Org. Chem.* **1991**, *56*, 2523
Keywords: Rearrangement

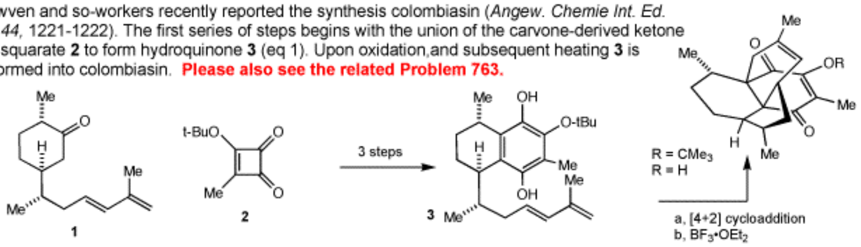
Please provide a mechanism for the following transformation (*JOC*, **1991**, *56*, 2523).



## Problem 762

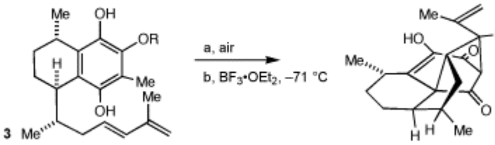
Contributer: **David A. Evans**
Citation: *Angew. Chem.* **2005**, *44*, 1221-1222
Keywords: Rearrangement

Harrowven and so-workers recently reported the synthesis colombiasin (*Angew. Chemie Int. Ed.* **2005**, *44*, 1221-1222). The first series of steps begins with the union of the carvone-derived ketone **1** and squarate **2** to form hydroquinone **3** (eq 1). Upon oxidation,and subsequent heating **3** is transformed into colombiasin. **Please also see the related Problem 763.**



**Problem 762.** Using your general knowledge of organic chemistry, illustate the reactions and reagents needed to transform **1** and **2** into **3**. Please provide reasonable mechanisms for each of the steps

**Problem 763.** In an earlier study, Rychnovsky and co-workers demonstrated that structures related to **3** (R = Me) could be transformed innto the biogenetically related natural product elisapterosin (**4**) by treatment with $BF_3$•$OEt_2$ (*Angew. Chemie Int. Ed.* **2003**, *42*, 1267-1270).



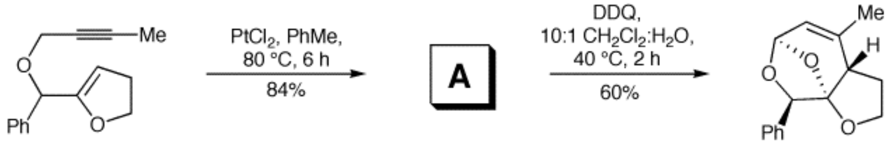
Elisapterosin (**4**)

Provide a mechanism for this transformation.

## Problem 765

Contributer: **Ryan Shenvi**
Citation: *Organic Lett.* **2004**, *6*, 3191
Keywords: Rearrangement

Based on the pioneering work of Murai (*Organometallics* **1996**, *15*, 901) and Fürstner (*J. Am. Chem. Soc.* **2000**, *122*, 6785-6786), Echavarren and co-workers (*Org. Lett.* **2004, *6***, 3191) demonstrated the interesting sequence of transformations shown below.

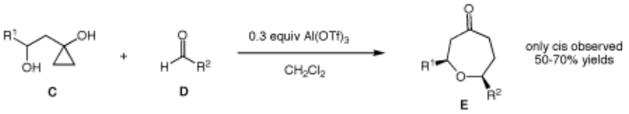


Please show the correct structure of compound **A** and delineate a mechanism for each transformation.

## Problem 767

Contributer: **Karl Scheidt**
Citation: *Organic Lett.* **2005**, *7*, 515
Keywords: Rearrangement

Ring expansions can drive reactions to provide interesting products. In recent work by Minbiole and coworkers (*Org. Lett.* **2005**, *7*, 515), the combination of cyclopropane alcohol **C** and aldehydes **D** affords the seven membered rings (**E**) with catalytic quantities of Lewis acids. Provide a mechanism for this process that accounts for the observed cis-diastereoselectivity.

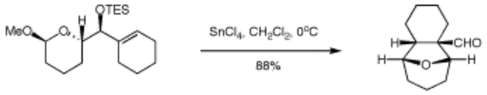


Your Answer:

## Problem 768

Contributer: **Karl Scheidt**
Citation: *Organic Lett.* **2004**, *6*, 3853
Keywords: Rearrangement

Using clear 3D representations, provide a mechanism for the transformation below. (*Org. Lett.* **2004**, *6*, 3853)

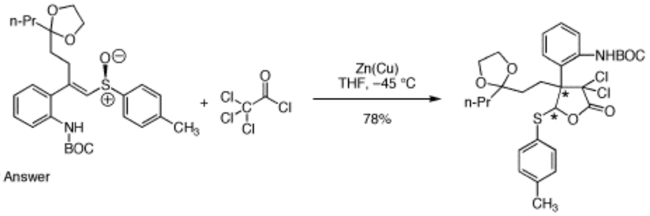


Your Answer:

## Problem 769

Contributer: **Karl Scheidt**
Citation: *J. Am. Chem. Soc.* **2002**, *124*, 13399
Keywords: Rearrangement

In a recent synthesis of (+)-aspidospermidine by Marino (*J. Am. Chem. Soc.* **2002**, *124*, 13399), a highly diastereoselective transformation was employed utilizing sulfur to afford the γ-butyrolactone product. (shown below). Provide a detailed mechanism for this process and indicate the stereochemistry of any newly formed asymmetric centers. HINT: The Zn(Cu) reagent is a 2 electron donor that is mixed with the trichloroacetyl chloride prior to the addition of the sulfoxide.

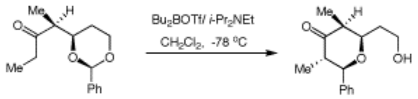


Your Answer

## Problem 770

Contributer: **Karl Scheidt**
Citation: *Organic Lett.* **2004**, *6*, 123
Keywords: Rearrangement

Please provide a rationale for the stereoselective synthesis of cyclic ethers in a single step shown by Sinha and coworkers (*Org. Lett.* **2004**, *6*, 123). Be sure to provide clear 3D drawing to account for the observed stereoselectivity. (Note: An excess of Bu$_2$BOTf (> 2 equiv) is necessary for the reaction to proceed.)

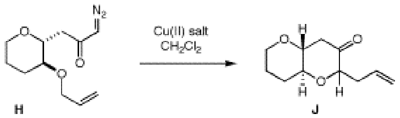


Your Answer:

## Problem 771

Contributer: **Karl Scheidt**
Citation: *J. Am. Chem. Soc.* **2001**, *123*, 5144
Keywords: Rearrangement

The synthesis of tetrahydropyrans is an important goal in access bioactive natural products. In a dislosure by West and Marmsäter (*J. Am. Chem. Soc.* **2001**, *123*, 5144), the conversion of **H** to **J** proceeds with good yield in the presence of Cu(II) catalysts. Indicate which stereoisomer is formed and provide a mechanism for this reaction which includes a rationale for the observed diastereoselectivity.



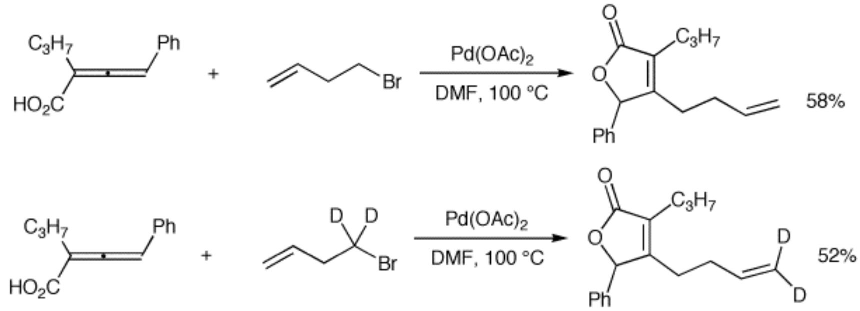
diastereoselectivity >30:1
80% yield

Your Answer:

## Problem 775

Contributer: **Ryan Ashok Shenvi**
Citation: *Angew. Chem.* **2003**, *42*, 1955
Keywords: Rearrangement

In a study of the Pd-mediated coupling reaction of 2,3-allenoic acids with ω-1-alkenyl halides, compound **1** was formed as the major product in 58% yield (*Angew. Chem. Int. Ed.*, **2003**, *42*, 1955). When the deuterium labeled substrate **2** was subjected to the same reaction conditions, product **3** was obtained in 52% yield.

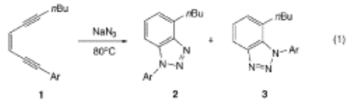


Propose a reasonable mechanism for the transformation that explains the fate of the deuterium atoms.

## Problem 779

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2005**, *7*, 475-477
Keywords: Rearrangement

The reaction of the illustrated ene-diyne **2** with sodium azide at 80 °C affords the benztriazoles **2** and **3**.(Org. Lett. **2005,** *7*, 475-477.

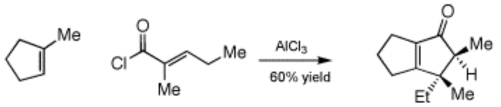


Provide plausible mechanisms for this transformation.

## Problem 780

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1991**, *113*, 8062-8069
Keywords: Rearrangement

Santilli and co-workers reported this Lewis acid catalyzed reaction (Santilli etal. *JACS* **1991, 113,** 8062-8069).

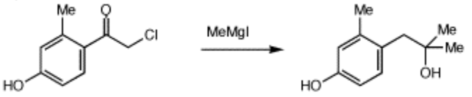


Please provide a reasonable mechanism for this transformation that includes the rationalization of the stereochemical outcome of the transformation.

## Problem 782

Contributer: **Ian Fleming**
Citation: *Tetrahedron Lett.* **1972**, 895
Keywords: Rearrangement

Bohlmann and Kapteyn treated the ketone with MeMgI and obtained an unexpected product (*Tetrahedron Lett.*, **1972,** 1895.).



Account for the formation of this product.

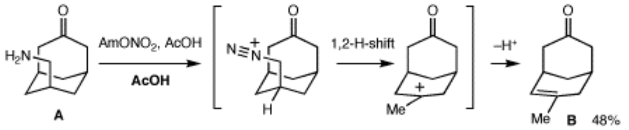
The α-chloroketone is susceptible to a Favorskii-like step **B**, because the removal of the proton from the phenolic oxygen **A** is easy, setting up an extended enolate. The opening of the cyclopropanone **C** is also easy and highly (a) chemo- and (b) regioselective. (a) The cyclopropanone carbonyl is more electrophilic than the other carbonyl group, because it is exocyclic to a strained ring, and not conjugated. (b) Although cyclopropanones in Favorskii reactions usually open to the less-substituted side, the charge on the more-substituted side in this case is largely taken up on the phenolic oxygen, and simultaneously the aromatic ring is restored.

It is possible, but unlikely, that the Grignard attacks the ketone *before* cyclopropanone formation, but the removal of the proton from the phenolic oxygen is likely to be fast, and conjugation between the phenolate and the ketone carbonyl would make the carbonyl group less electrophilic.

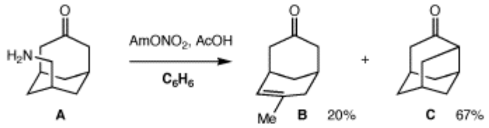
## Problem 784

Contributer: **Ian Fleming**
Citation: *J. Org. Chem.* **1973**, *38*, 3462
Keywords: Rearrangement

Primary amines on treatment with nitrous acid give diazonium ions. These reactive intermediates are only isolated when the amine is aromatic. With aliphatic amines, the diazonium ion is a reactive intermediate which usually undergoes elimination or substitution reactions, sometimes preceded by cationic rearrangement. This was the result with the primary amine **A** when the reaction was carried out in acidic solution: the unsaturated ketone **B** was the major product (J.-H. Liu and P. Kovacic, *J. Org. Chem.*, 1973, **38**, 3462).



However, Liu and Kovacic found that, when the amount of acid was limited to one molar equivalent, the major product was the saturated ketone **C**.

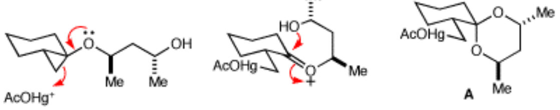


Account for the formation of the ketone **C**.

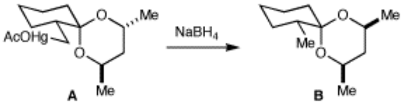
## Problem 785

Contributer: **Ian Fleming**
Citation: *Tetrahedron Lett.* **1993**, *34*, 505
Keywords: Rearrangement

Mercuric ions are soft electrophiles, which attack alkenes and even cyclopropanes, as in the reaction forming the organomercury intermediate **A**:



Normally the mercury is removed by reduction with sodium borohydride in a radical chain reaction. In the case of the mercury derivative A, however, Sugimura found that an unexpected change in configuration in the 1,3-dioxan ring took place when this reaction was carried out on the mercury compound **A**, giving the product **B** (T. Sugimura, S. Goto, K. Koguro, T. Futagawa, S. Misaki, Y, Morimoto, N. Yasuwaka and A. Tai, *Tetrahedron Lett.*, **1993,** *34*, 505).

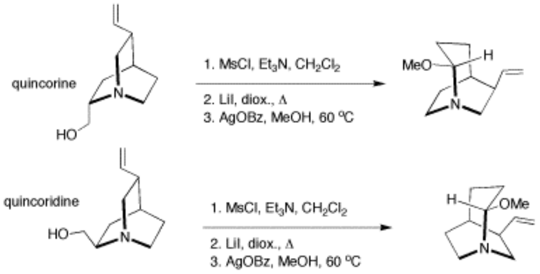


Explain this result.

## Problem 786

Contributer: **Robert M. Williams**
Citation: *Organic Lett.* **2000**, *2*, 1661
Keywords: Rearrangement

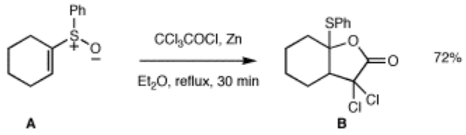
Hoffman, et al., reported the interesting ring expansion reaction of azabicyclo[2.2.2]octanes as shown below. Please provide a mechanistic rationalization for this transformation. Note that complete stereospecificity is observed from the two diastereomers quincorine and quincoridine; your mechanism should account for the observed stereospecificity.
(Roper, S.; Frackenpohl, J.; Schrake, O.; Wartchow, R.; Hoffmann, M.R., *Org. Lett.* **2000**, *2*, 1661; Roper, S.; Wartchow, R.; Hoffmann, M.R., *Org. Lett.* **2002**, *4*, 3179)



## Problem 787

Contributer: **Ian Fleming**
Citation: *J. Am. Chem. Soc.* **1981**, *103*, 7687
Keywords: Rearrangement

The sulfoxide **A** gives the lactone **B** when treated with trichloroacetyl chloride and zinc (J. P. Marino and M. Neisser, *J. Am. Chem. Soc.*, **1981**, *103*, 7687).

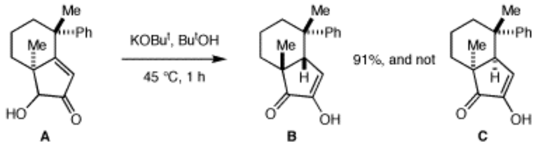


Explain this result.

## Problem 788

Contributer: **Ian Fleming**
Citation: *J. Org. Chem.* **1970**, *35*, 570
Keywords: Rearrangement

In the base-catalyzed isomerization of the α-hydroxyketone **A** to the enol **B** of an α-diketone, Ireland found that the stereochemistry at the methyl-bearing carbon had unexpectedly changed (R. E. Ireland, P. S. Grand, R. E. Dickerson, J. Bordner and D. R. Rydjeski, *J. Org. Chem.*, **1970**, *35*, 570).

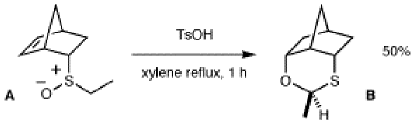


Ireland separately prepared the ketone **C**, which he had expected, and found that this was stable to the reaction conditions. Bearing in mind that **C** was not an intermediate, explain both how and why this isomerization occurred.

## Problem 790

Contributer: **Ian Fleming**
Citation: *Chem. Commun.* **1995**, 1197
Keywords: Rearrangement

The sulfoxide **A** isomerizes to the mixed acetal **B** on treatment with acid (H. Abe, J. Itani, C. Masunari, S. Kashino and T. Harayama, *Chem. Commun.*, **1995**, 1197).

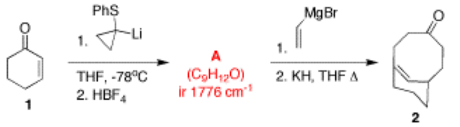


Explain this result.

## Problem 792

Contributer: **Robert M. Williams**
Citation: *Tetrahedron Lett.* **1980**, *21*, 4547
Keywords: Rearrangement

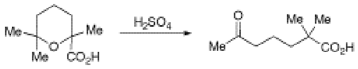
Kahn reported the interesting pleuromutilin model study shown below (*Tetrahedron Lett.* **1980**, *21*, 4547). Propose a mechanism for the transformation of **1** into "**A**" and the mechanism for the conversion of **A** into **2** and provide the structure for **A**.



## Problem 793

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1960**, *82*, 483-486
Keywords: Rearrangement

The rearrangement of **1** to **2** was discovered by Rupe and Liechtenhan (*Ber.* **1908**, *41*, 1278). At that time, the transformation attracted attention as a consequence of the *apparent* long-range migration of a methyl group. Meinwald and co-workers (*JACS* **1960**, 82, 483) ultimately provided strong experimental evidence for the mechanism of this rearrangement.



α–cinenic acid (**1**)

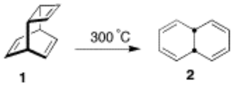
geronic acid (**2**)

Provide a mechanism for this transformation and suggest experiments that might be carried out to support your proposal.

## Problem 794

Contributer: **Robert M. Williams**
Citation: *J. Am. Chem. Soc.* **1966**, *88*, 2078-2079
Keywords: Rearrangement

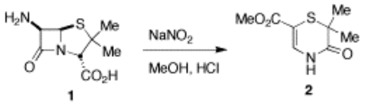
Doering and Rosenthal reported the interesting conversion of Nenitzescu's hydrocarbon (**1**) to dihydro-naphthalene (**2**). Provide a mechanistic rationalization for this transformation. (Reference: Doering, W.v.E.; Rosenthal, J.W., *J.Am.Chem. Soc.* **1966**, *88*, 2078-2079)



## Problem 795

Contributer: **Robert M. Williams**
Citation: *Tetrahedron Lett.* **1967**, 941-945
Keywords: Rearrangement

Treatment of 6-amino-penicillanic acid (**1**) with sodium nitrite in aqueous methanolic HCl, leads to the interesting heterocycle, 2,3-dihydro-1,4-thaizin-3-one (**2**). Provide a mechanistic rationalization.
(Reference: Stoodley, R.J. *Tetrahedron Lett.* **1967**, 941-945)



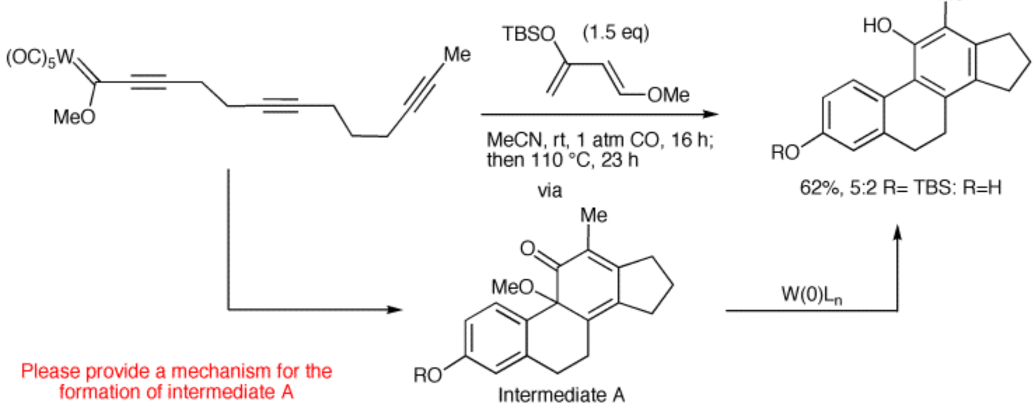
**1** **2**

***Answer:***

## Problem 796

Contributer: **Dan O'Malley**
Citation: *J. Am. Chem. Soc.* **1994**, *116*, 7616
Keywords: Rearrangement

In their studies on tungsten carbonyl chemistry, Wulff and co-workers discovered a way to construct all four rings of the steroid skeleton in a single cascade (*JACS*, **1991**, *113*, 9873, *JACS*, **1994**, *116*, 7616). The final step of the reaction is the tungsten mediated reduction of intermediate A.

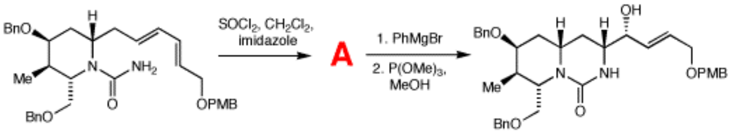


Please provide a mechanism for the formation of intermediate A

## Problem 812

Contributer: **Achanta Srinavas**
Citation: *J. Am. Chem. Soc.* **2002**, *124*, 3939
Keywords: Rearrangement

As a pivotal step in the synthesis of the freshwater cyanobacterial hepatoxin cylindrospermopsin, Weinreb and co-workers carried out the following transformation *(JACS,* **2002,** *124*, 3939).

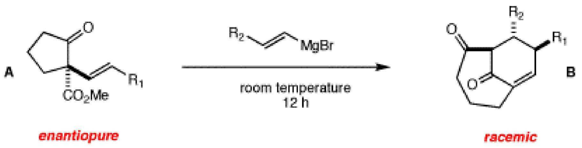


Provide a mechanism for the overall transformation and identify **Intermediate A**.

## Problem 813

Contributer: **Regan Thomson**
Citation: *Angew. Chem.* **2005**, *44*, 2259
Keywords: Rearrangement

The key step in Shair's total synthesis of CP-263-114 involved a one-pot synthesis of the bridged bicyclic system using a cascade sequence initiated by a Grignard addition to a β-keto ester. During the course of these studies it was found that if the reaction of enantiopure β–keto ester **A** was allowed to proceed at room temperature for 12 h then the product **B** was obtained as a single diastereomer but as a *racemic mixture*.

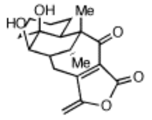


Using clear three-dimensional drawings provide an overall mechanism for the transformation shown above that accounts for both the observed diasteroselectivity as well as the formation of the product as a racemate.

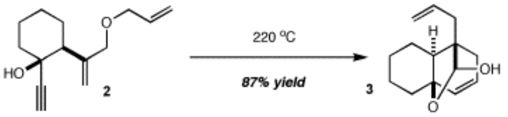
## Problem 815

Contributer: **Jillian Spangler**
Citation: *Organic Lett.* **2005**, *7*, 4589
Keywords: Rearrangement

As part of a strategy directed towards the synthesis of tetradecamycin **(1)**, Warrington and Barriault carried out the thermally induced rearrangement of **2** to synthesize the *trans*-decalin system **3** (*Org. Lett.* **2005**, *7*, 4589). Using clear three-dimensional drawings please provide a plausible mechanism for this transformation that is in accordance with the observed stereochemical outcome.



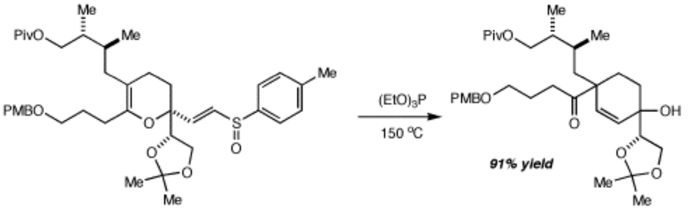
tetradecamycin (**1**)



## Problem 816

Contributer: **Regan Thomson**
Citation: *Organic Lett.* **2005**, *7*, 1629
Keywords: Rearrangement

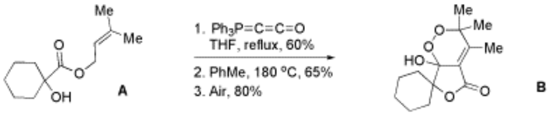
As part of a program directed toward the synthesis of the pinnatoxins, Pelc and Zakarian reported the single-pot conversion of sulfone **A** into cyclohexene **B** (*OL*, **2005**, *7*, 1629). Using clear three-dimensional representations please provide a concise mechanism for this transformation and predict the relative stereochemical outcome.



## Problem 822

Contributer: **Christos Mitsos**
Citation: *J. Chem. Soc. Perkin Trans 1* **2003**, *68*, 9827-9830
Keywords: Rearrangement

Schobert and co-workers recently reported an interesting series of events when reacting prenyl ester **A** under the given conditions (R. Schobert *et al*, *Tetrahedron Lett.* **2001**, *42*, 4561-4564; R. Schobert *et al*, *J. Org. Chem.* **2003**, *68*, 9827-9830).

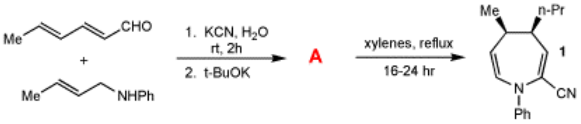


Please delineate a rational mechanism to convert **A** into **B**.

## Problem 828

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1989**, *54*, 481-484
Keywords: Rearrangement

Fang and co-workers reported the following series of transformations (*J. Org. Chem.* **1989**, *54*, 481-484).

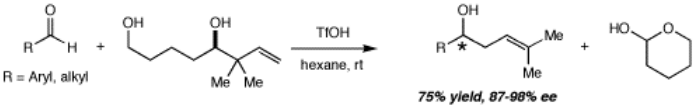


The indicated three-step process leads to the production of enamine **1**. Propose a mechanism for the overall transformation that includes the structure of intermediate **A**.

## Problem 829

Contributer: **Regan Thomson**
Citation: *J. Am. Chem. Soc.* **2003**, *125*, 4990
Keywords: Rearrangement

The prenyl group is an essential unit in the biosynthesis of terpene natural products. Due to the large number of natural products that contain this moiety, methods for its selective introduction into molecules are highly useful. Loh and Cheng have descibed a general regioselective and highly enantioselective prenylation of aldehydes, as shown below (*JACS* **2003**, *125*, 4990).

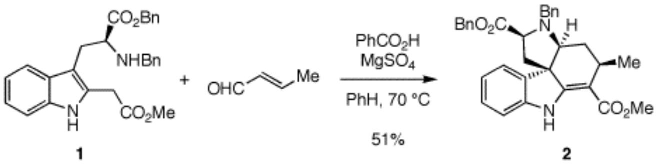


Please provide a general mechanism for this interesting reaction and using clear three-dimensional drawings predict the absolute stereochemical outcome.

## Problem 831

Contributer: **Mohammad Movassaghi**
Citation: *J. Org. Chem.* **1997**, *62*, 7950-790
Keywords: Rearrangement

Kuehne reported an efficient synthesis of the ABCD ring system of strychnos alkaloids via the conversion of the amino diester **1** to the tetracycle **2** (*JOC* **1997**, *62*, 7950-7960) . Provide a mechanism for this transformation.

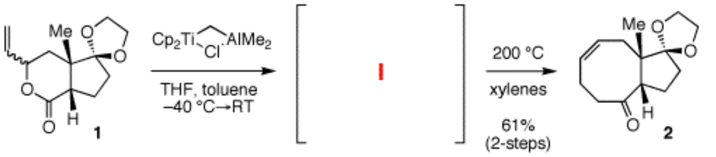


**ANSWER:**

## Problem 832

Contributer: **Mohammad Movassaghi**
Citation: *J. Am. Chem. Soc.* **1993**, *115*, 1676-1683
Keywords: Rearrangement

The following transformation served as a key step in Paquette's synthesis of (+)-ceroplastol I (*JACS* **1993**, *115*, 1676-1683). Identify the intermediate **I** and clearly explain the formation of ketone **2** from lactone **1**.

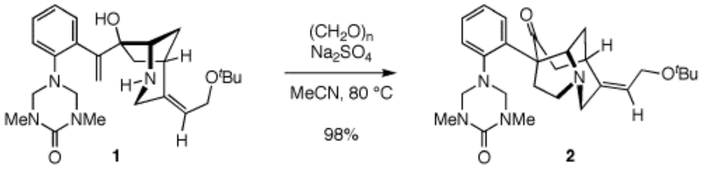


**ANSWER:**

## Problem 833

Contributer: **Mohammad Movassaghi**
Citation: *J. Am. Chem. Soc.* **1993**, *115*, 9293-9294
Keywords: Rearrangement

The following transformation served as a highly effective step in Overman's elegant total synthesis of (−)-strychnine (*JACS* **1993**, *115*, 9293-9294). Provide a mechanism for the conversion of amino alcohol **1** to the ketone **2.**

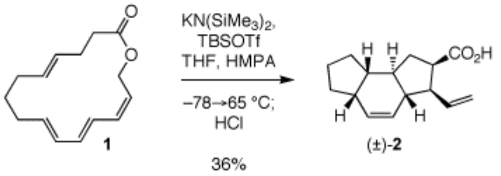


**ANSWER:**

## Problem 834

Contributer: **Mohammad Movassaghi**
Citation: *Can J. Chem* **2000**, *78*, 757-771
Keywords: Rearrangement

During studies directed toward the total synthesis of spinosyn A, Roush reported the synthesis of the decahydro-*as*-indacene ring system present in tricycle **2** (*Can. J. Chem.* **2000**, *78*, 757-771). Provide a reasonable mechanism for the conversion of lactone **1** to the carboxylic acid **2**.

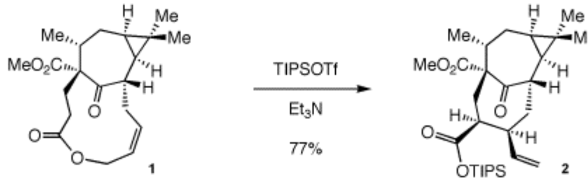


**ANSWER:**

## Problem 835

Contributer: **Mohammad Movassaghi**
Citation: *J. Am. Chem. Soc.* **110**, *110*, 3298-3300
Keywords: Rearrangement

During studies related to the synthesis of ingenol, Funk reported the conversion of lactone **1** to the silyl ester **2** (*JACS* **1988**, *110*, 3298-3300). Provide a mechanism for this transformation and clearly account for the observed stereochemistry in the product **2**.

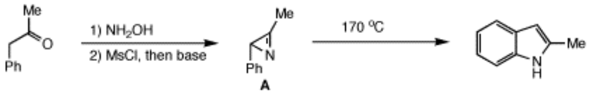


**ANSWER:**

## Problem 837

Contributer: **Keith Fandrick**
Citation: *J. Am. Chem. Soc.* **2006**, *ASAP*,
Keywords: Rearrangement

Taber recently reported the synthesis of substituted indoles utilizing the Neber reaction. The reaction shown below is a representative example of the reaction sequence. (*JACS*, **2006**, *128*, 1058).



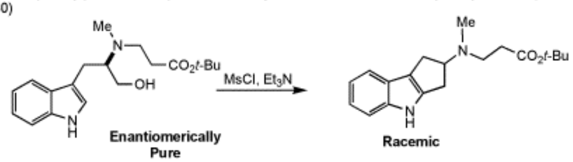
**Part A.** In the space provided show a reasonable mechanism for the conversion of the ketone into the intermediate azirine **A**.

**Part B.** In the space provided show a reasonable mechanism for the conversion of the intermediate azirine to the corresponding indole product.

## Problem 839

Contributer: **Keith Fandrick**
Citation: *Tetrahedron Lett.* **1993**, 439
Keywords: Rearrangement

The mechanism for the substitution of 3-substituted indoles at the C-2 position has been debated for sometime. During Heathcock's synthesis of Lysergic acid the following oberservation was made. The starting material was derived from tryptophan and is optically pure. But the product of the cyclization was found to be optically inactive (racemic). (*Tet. Lett.* **1993**, 439-440)

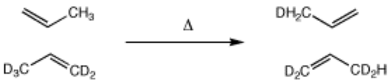


In the space provided provide a mechanism that is consistent with the above oberservations.

## Problem 846

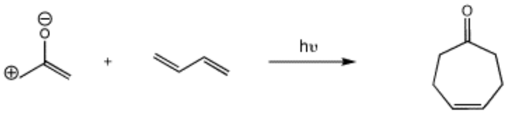
Contributer: **Pavel Nagorny**
Citation:
Keywords: Rearrangement

For the process indicated below please use either the Dewar Zimmerman or FMO analysis to predict whether isotope scrambling is allowed under thermal conditions.



**Your Answer:**

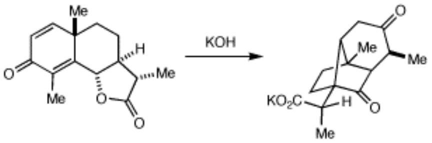
**Part B**. Using FMO analysis, please predict whether the following cycloaddition is allowed under photochemical conditions.



## Problem 851

Contributer: **Regan Thomson**
Citation: *J. Am. Chem. Soc.* **1948**, *70*, 4216
Keywords: Rearrangement

Woodward and coworkers reported the following base-promoted conversion of $\alpha$-santonin into potassium santanoate as part of a classic natural product structural determination (*JACS* **1948**, *70*, 4216). In the space below please provide a concise mechanism for this intriguing rearrangement.
*Hint: Work on the analysis of this transformation bi-directionally.*

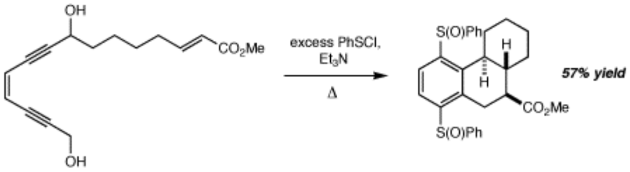


**Your Answer:**

## Problem 853

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2006**, *8*, 95
Keywords: Rearrangement

The following cascade reaction to convert a linear precursor into a complex tricyclic structure was very recently reported (*Org. Lett.* **2006**, *8*, 95). In the space below please provide a detailed mechanism for this reaction. Be sure to account for the observed sterochemical outcome and to clearly label any pericyclic processes.



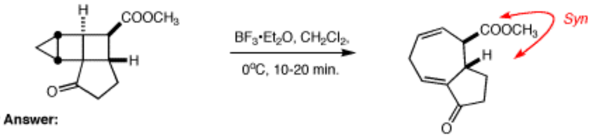
**Your Answer:**

## Problem 854

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2005**, *7*, 5785
Keywords: Rearrangement

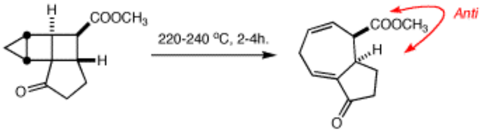
Snapper and co-workers have recently identified a mild, Lewis acid-mediated fragmentation of cyclobutane-containing adducts as a rapid entry into bicyclo[5.3.0]decane ring systems (*Org. Lett.* **2005**, *7*, 5785). They also noted that the stereochemical outcome of the acid-mediated fragmentations in such systems is complementary to the observed thermal ring expansions.

**Part 1.** Please provide a plausible mechanism for the following Lewis acid-mediated transformation.



**Your Answer:**

**Part 2.** Propose a mechanism that rationalizes the complementry stereochemical outcome of the following thermal rearrangement.

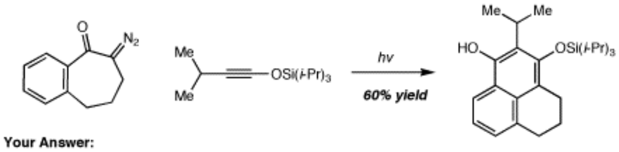


**Your Answer:**

## Problem 855

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1990**, *112*, 3093
Keywords: Rearrangement

As part of a study directed towards the synthesis of the natural product Hyellazole, Danheiser and coworkers developed a clever route to the synthesis of complex fused polycyclic structures (*JACS* **1990**, *112*, 3093). Please provide a mechanism for the following rearrangement. Be sure to label all relevant pericyclic rarrangements.

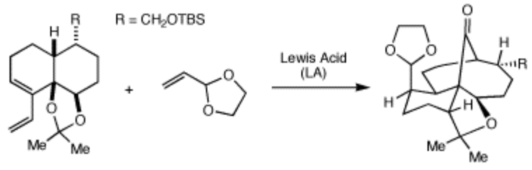


**Your Answer:**

## Problem 856

Contributer: **Meredth McGowen**
Citation: *Organic Lett.* **2005**, *7*, 5921
Keywords: Rearrangement

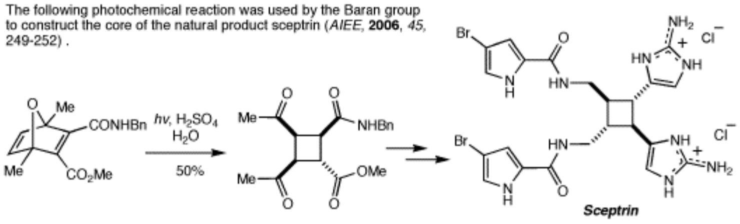
Barriault recently published the following Lewis-acid mediated reaction cascade as a strategy to rapidly assemble highly functionalized bicycloalkanones (*Org. Lett.* **2005**, *7*, 5921). Using clear 3D representations, please provide a mechanism that includes a rationalization for the relative stereochemistry observed in the product.



## Problem 857

Contributer: **David A. Evans**
Citation: *Angew. Chem.* **2006**, *45*, 249-252
Keywords: Rearrangement

The following photochemical reaction was used by the Baran group to construct the core of the natural product sceptrin (*AIEE*, **2006**, *45*, 249-252) .

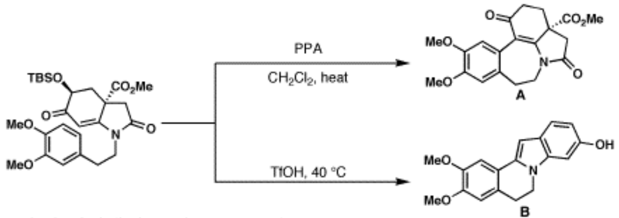


In the space below please provide a reasonable mechanism for this powerful, multistep transformation.

## Problem 861

Contributer: **David Lin**
Citation: *Organic Lett.* **2006**, *8*, 601-604
Keywords: Rearrangement

While developing a route to the synthesis of Erythrina alkaloids, Padwa and colleagues encountered the following transformations (Org. Lett. **2006**, *8*, 601-604).

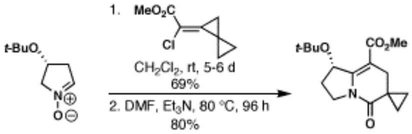


Propose a mechanism for both observed rearrangements.

## Problem 862

Contributer: **Ryan Shenvi**
Citation: *J. Org. Chem.* **2006**, *71*, 2417-2423
Keywords: Rearrangement

Alberto Brandi and co-workers recently reported the rearrangement of isoxazolidines to enantiopure indolizinones by way of the chemistry of halomethylcyclopropanes (*J. Org. Chem.*, **2006**, *71*, 2417-2423).

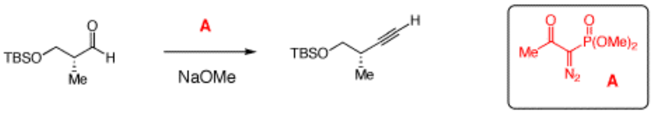


Please delineate a mechanism to arrive at the final product.

## Problem 866

Contributer: **Karl Scheidt**
Citation: *J. Am. Chem. Soc.* **2005**, *127*, 17921
Keywords: Rearrangement

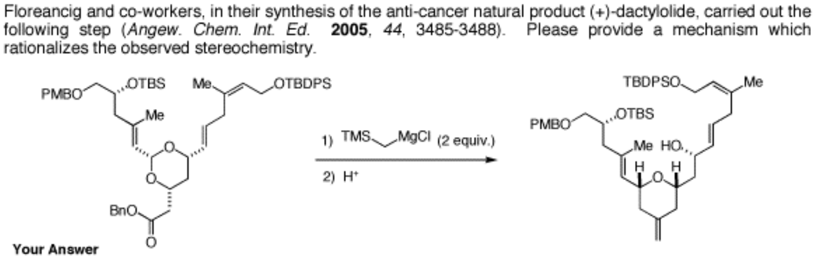
In the total synthesis of Amphidinolide P (*J. Am. Chem. Soc.* **2005**, *127*, 17921-17937), Trost and coworkers employed the Bestmann reagent (**A**) to synthesize the shown alkyne. Provide a mechanism for this step.



**Your Answer**

## Problem 869

Contributer: **Karl Scheidt**
Citation: *Angew. Chem.* **2005**, *44*, 3485-3488
Keywords: Rearrangement

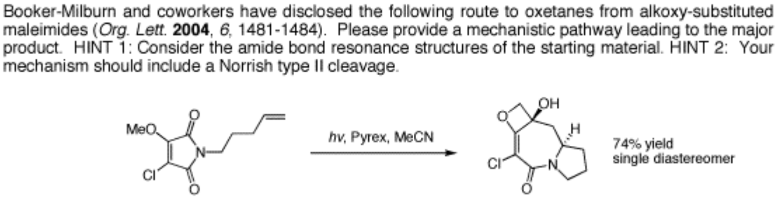


Floreancig and co-workers, in their synthesis of the anti-cancer natural product (+)-dactylolide, carried out the following step (*Angew. Chem. Int. Ed.* **2005**, *44*, 3485-3488). Please provide a mechanism which rationalizes the observed stereochemistry.

**Your Answer**

## Problem 870

Contributer: **Karl Scheidt**
Citation: *Organic Lett.* **2004**, *6*, 1481-1484
Keywords: Rearrangement

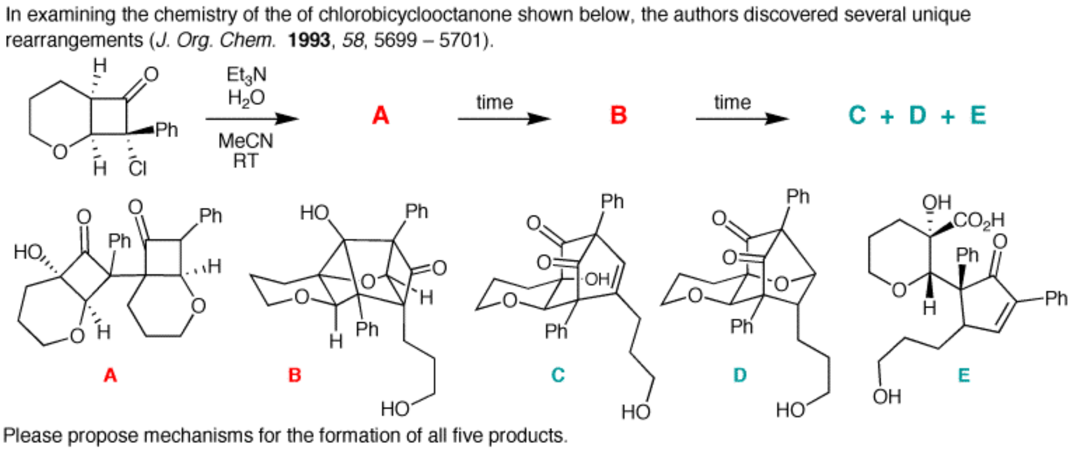


Booker-Milburn and coworkers have disclosed the following route to oxetanes from alkoxy-substituted maleimides (*Org. Lett.* **2004**, *6*, 1481-1484). Please provide a mechanistic pathway leading to the major product. HINT 1: Consider the amide bond resonance structures of the starting material. HINT 2: Your mechanism should include a Norrish type II cleavage.

**Your Answer**

## Problem 872

Contributer: **Jeremy Richter**
Citation: *J. Org. Chem.* **1993**, *58*, 5699-5701
Keywords: Rearrangement

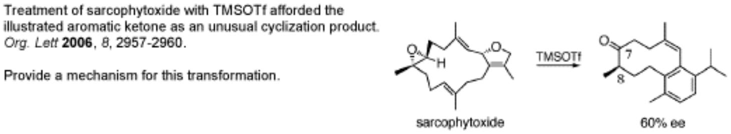


In examining the chemistry of the of chlorobicyclooctanone shown below, the authors discovered several unique rearrangements (*J. Org. Chem.* **1993**, *58*, 5699 – 5701).

Please propose mechanisms for the formation of all five products.

## Problem 874

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2006**, *88*, 2957-2960
Keywords: Rearrangement



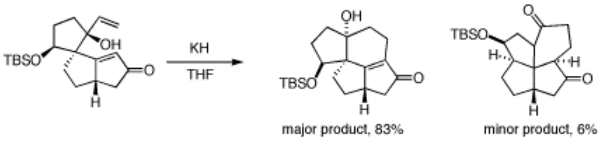
Treatment of sarcophytoxide with TMSOTf afforded the illustrated aromatic ketone as an unusual cyclization product. *Org. Lett* **2006**, *8*, 2957-2960.

Provide a mechanism for this transformation.

## Problem 875

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2006**, *88*, 3195-3198
Keywords: Rearrangement

Burnell and Thornton have recently disclosed the following base induced transformation (*Org. Lett.* **2006**, *8*, 3195-3198). The structures of both products were secured by X-ray analysis.

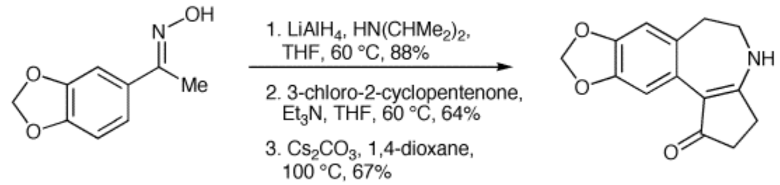


Please provide a rational mechanism leading to the major and minor products.

## Problem 877

Contributer: **Karl Scheidt**
Citation: *J. Am. Chem. Soc.* **2006**, *128*, ASAP
Keywords: Rearrangement

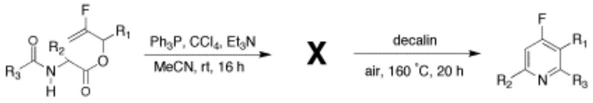
Gin and co-workers (*JACS* **2006**, *128*, ASAP) recently reported the following set of transformations during the total synthesis of the anti-Leukemia alkaloid (–)-deoxyharrington. Provide the mechanisms for the following series of reactions.


N
OH
Me
1. LiAlH$_4$, HN(CHMe$_2$)$_2$, THF, 60 °C, 88%
2. 3-chloro-2-cyclopentenone, Et$_3$N, THF, 60 °C, 64%
3. Cs$_2$CO$_3$, 1,4-dioxane, 100 °C, 67%
NH
O

## Problem 878

Contributer: **Jun Shi**
Citation: *Synthesis* **2006**, 2058-2096
Keywords: Rearrangement

While developing a synthetic route to 4-Fluoropyridines, Ulrich Wittmann and Colleagues encountered the following transformation (*Synthesis* **2006**, *13*, 2058–2096).



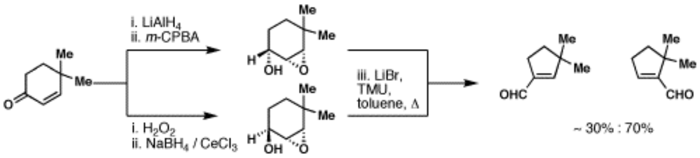
R$_1$=H, R$_2$=Ph, R$_3$=Ph

Please provide a reasonable mechanism for this set of transformations and Identify **X**.

## Problem 895

Contributer: **Moritz Biskup**
Citation: *J. Org. Chem.* **1986**, *51*, 212-217
Keywords: Rearrangement

In studies directed toward the syntheses of terpenes, G. Magnusson *et al.* investigated the preparation α,β-unsaturated cyclopentenals from six-membered precursors (*J.Org.Chem.* **1986**, *51*, 212-217). The reaction was studied in detail and the postulated mechanism rationalizes the observed product formation.

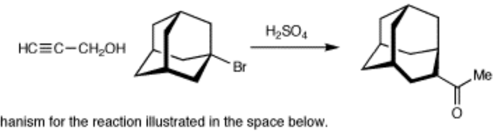


Please provide a plausible mechanism for the formation of the indicated products.

## Problem 897

Contributer: **David A. Evans**
Citation: *Chem. Commun.* **1971**, 533
Keywords: Rearrangement

The following bromoadamantane reaction with propargyl alcohol has been reported (Chem Commun. 1971, 533).

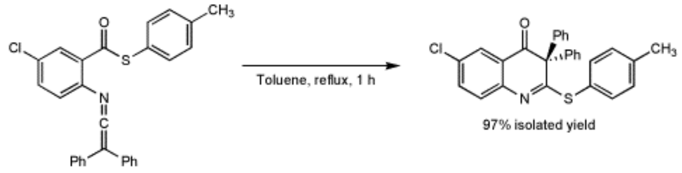


Provide a mechanism for the reaction illustrated in the space below.

## Problem 904

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2006**, *71*, 816
Keywords: Rearrangement

The quinolinone synthesis depicted below was recently reported by Alajarin and coworkers (*J. Org. Chem.* **2006**, *71*, 8126-8139). Please provide a mechanism for this transformation.

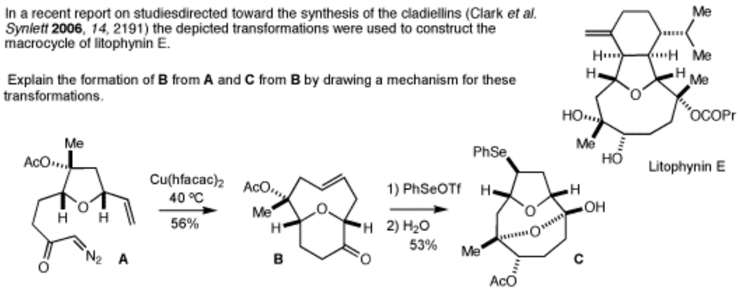


## Problem 905

Contributer: **Pavel Nagorny**
Citation: *SynLett* **2006**, *14*, 2191
Keywords: Rearrangement

In a recent report on studiesdirected toward the synthesis of the cladiellins (Clark *et al.* *Synlett* **2006**, *14*, 2191) the depicted transformations were used to construct the macrocycle of litophynin E.

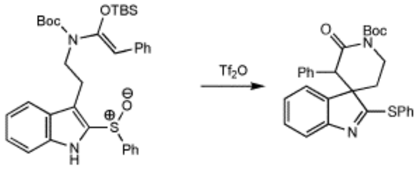
Explain the formation of **B** from **A** and **C** from **B** by drawing a mechanism for these transformations.



## Problem 907

Contributer: **Hyun-Ji Song**
Citation: *Organic Lett.* **2004**, *6*, 1869-1871
Keywords: Rearrangement

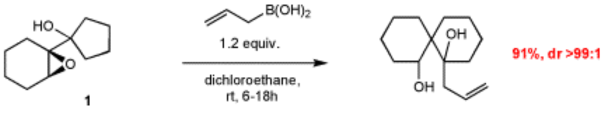
In 2004, Feldman and coworker published a construction of 3,3-spirosubstituted oxindoles. (*Org. Lett.* **2004**, *6*, 1869-1871). Provide the reaction mechanism and use it to predict the product relative stereochemistry. Explain the origins of diastereoselectivity using clear 3D drawings.



## Problem 909

Contributer: **Christian Markert**
Citation: *Angew. Chem.* **2004**, *43*, 1702
Keywords: Rearrangement

Tu *et al.* reported the following useful construcion that could be used for a diastereoselective generation of the illustrated bicyclic structures with quarternary stereocenters. (*ACIEE* **2004**, *43*, 1702).

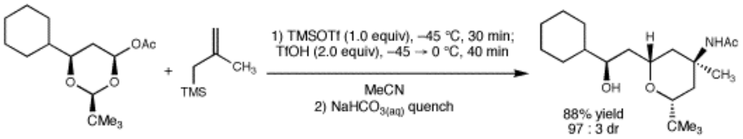


Please predict stereochemistry of the product and provide a mechanism that would support your predictions.

## Problem 913

Contributer: **Mathieu Lalonde**
Citation: *J. Am. Chem. Soc.* **2006**, *ASAP*,
Keywords: Rearrangement

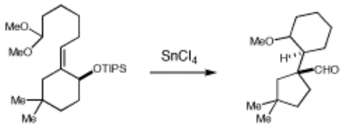
The transformation depicted below was recently reported by Rovis and coworkers (Epstein, O. L.; Rovis, T. *J. Am. Chem. Soc.* **2006**, ASAP). Provide a mechanism for this transformation that accounts for the observed diastereoselectivity.


OAc
O
O
CMe$_3$
+
CH$_3$
TMS
1) TMSOTf (1.0 equiv), –45 °C, 30 min;
TfOH (2.0 equiv), –45 → 0 °C, 40 min
MeCN
2) NaHCO$_{3(aq)}$ quench
H
NHAc
CH$_3$
OH
O
CMe$_3$
88% yield
97 : 3 dr

## Problem 915

Contributer: **Karl Scheidt**
Citation: *J. Org. Chem.* **2006**, *71*, 1581-1587
Keywords: Rearrangement

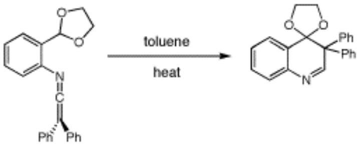
Overman has been a major contributor in the field of carbocation chemistry. In 2006, he observed that the following reaction proceeded with complete retention of absolute configuration (*J. Org. Chem.* **2006**, *71*, 1581-1587). Please provide a mechanism for this transformation which includes 3-dimensional structures and a rationale for the stereochemical outcome. Be sure to label all pericyclic processes.



## Problem 918

Contributer: **Karl Scheidt**
Citation: *Organic Lett.* **2006**, *81*, 5645-5648
Keywords: Rearrangement

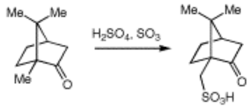
Alajarín and co-workers (*Org. Lett.* **2006**, *8*, 5645-5648) discovered when the following ketenimine is heated in toluene, a cyclization occurs. Please provide a detailed mechanism for this transformation. Be sure to label all pericyclic processes.



## Problem 922

Contributer: **Karl Scheidt**
Citation:
Keywords: Rearrangement

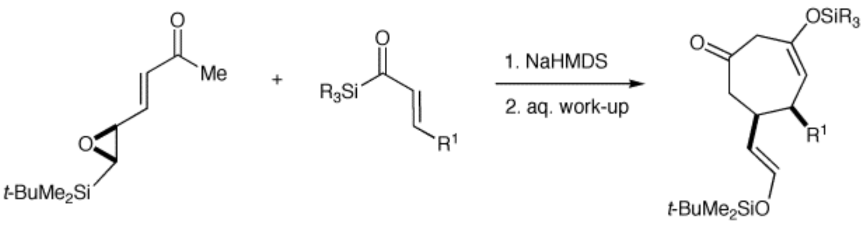
Camphor is prone to rearrangement when exposed to acid. Camphorsulfonic acid (CSA), which is a common reagent in organic synthesis, is formed when camphor is treated sulfuric acid and sulfur trioxide. Please provide a mechanism using 3-dimensional structures.



## Problem 923

Contributer: **Karl Scheidt**
Citation: *J. Org. Chem.* **2007**, *72*, 1379
Keywords: Rearrangement

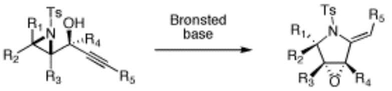
Takeda and coworkers recently reported the following formal [3+4] addition for the synthesis of 7-membered ketones (*J. Org. Chem.* **2007**, *72*, 1379). Please provide a mechansim for the generation of the product.



## Problem 926

Contributer: **Karl Scheidt**
Citation: *J. Am. Chem. Soc.* **2007**, *129*, 3794
Keywords: Rearrangement

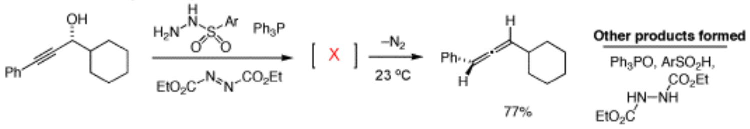
Generally, transition metal catalysis is used for the addition of an N–H group across a pi system (hydroamination). However, Borhan from Michigan State very recently reported a method to perform this reaction with no metal using a Brønsted base (*JACS*, **2007**, *129*, 3794-3795). Please provide a mechanism for this reaction.



## Problem 931

Contributer: **Karl Scheidt**
Citation: *J. Am. Chem. Soc.* **1996**, *118*, 4492
Keywords: Rearrangement

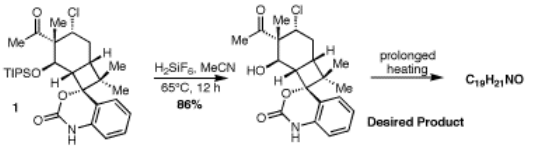
The Myers group published the following stereospecific synthesis of allenes from propargylic alcohols (*J. Am. Chem. Soc.* **1996**, *118*, 4492). Please provide a mechanism for this transformation that accounts for the stereochemistry of the product.



## Problem 932

Contributer: **Thomas Maimone**
Citation:
Keywords: Rearrangement

During their studies directed toward the total synthesis of welwitindolinone A, the Wood group observed the formation of an unusual aromatic heterocycle ($C_{19}H_{21}NO$) after removing the silyl protecting group of **1** (Sarah Reisman thesis, *Yale Univ. 2006*).

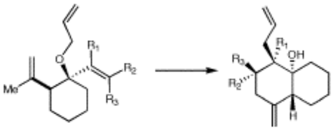


Propose a structure for the unknown heterocycle as well as a mechanism for its formation.

## Problem 933

Contributer: **Karl Scheidt**
Citation: *J. Am. Chem. Soc.* **2007**, *129*, 2112-2119
Keywords: Rearrangement

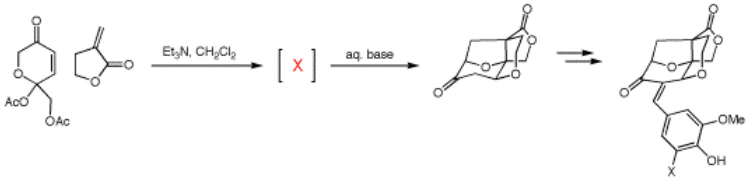
Louis Barriault is well known for orchestrating cascade reactions Here is an example from a recent paper (*J. Am. Chem. Soc.* **2007**, *129, 2112-2119).* Please provide a mechanism with 3-dimensional structures.



## Problem 936

Contributer: **Karl Scheidt**
Citation: *Organic Lett.* **2007**, *9*, 873-874
Keywords: Rearrangement

Snider and co-workers recently completed a formal synthesis of (±)-polygalolides A and B (*Org. Lett.* **2007**, *9*, 873-874). The main bond forming reaction forms **X**, which upon treatment with aqueous base, affords the core structure of the polygalolides. Please provide the structure of **X** and a mechanism for its formation.

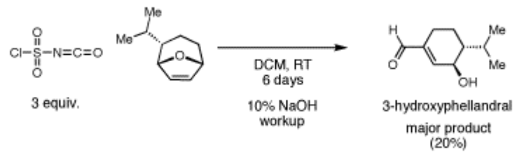


**(±)-polygalolides A and B**

## Problem 939

Contributer: **Paul Krawczuk**
Citation: *J. Chem. Soc. Perkin Trans 1* **1993**, 585-587
Keywords: Rearrangement

While working on oxa-analouges of the plant growth-promoting agent helminthosporal, Barbosa and coworkers encountered an unexpected rearangement when they treated the bicyclic alkene below with chlorosulfonyl isocyanate (CSI) (*J. Chem. Soc. Perkin Trans.* 1 **1993** 585-587).



**Answers**

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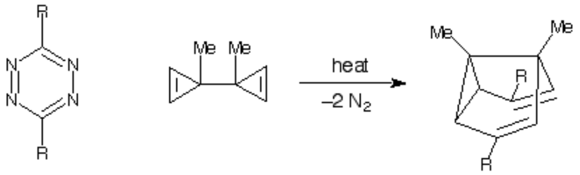
# Problem Answers

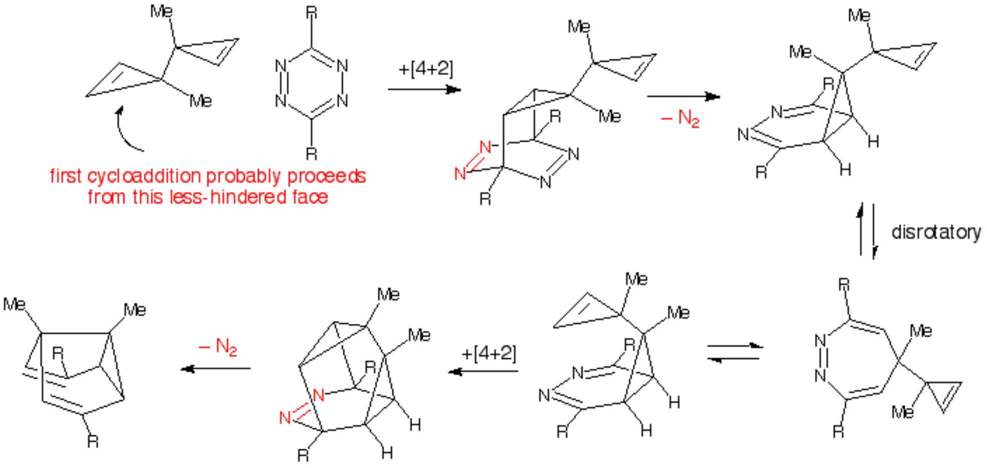
## Problem 1

Contributer: **David A. Evans**
Citation: *Eur, J. Chem.* **2002**, 791-801

The following "one-pot" synthesis of semibulvalene was recently reported by J. Sauer (*Eur. J. Chem.* **2002**, 791-801).



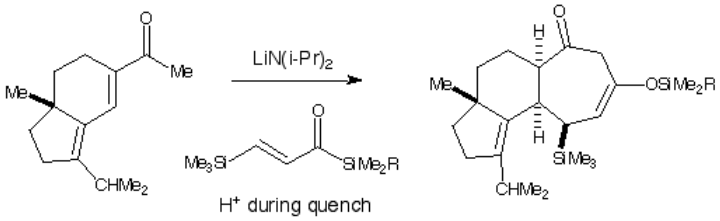
Provide a plausible mechanism for this transformation in the space below:



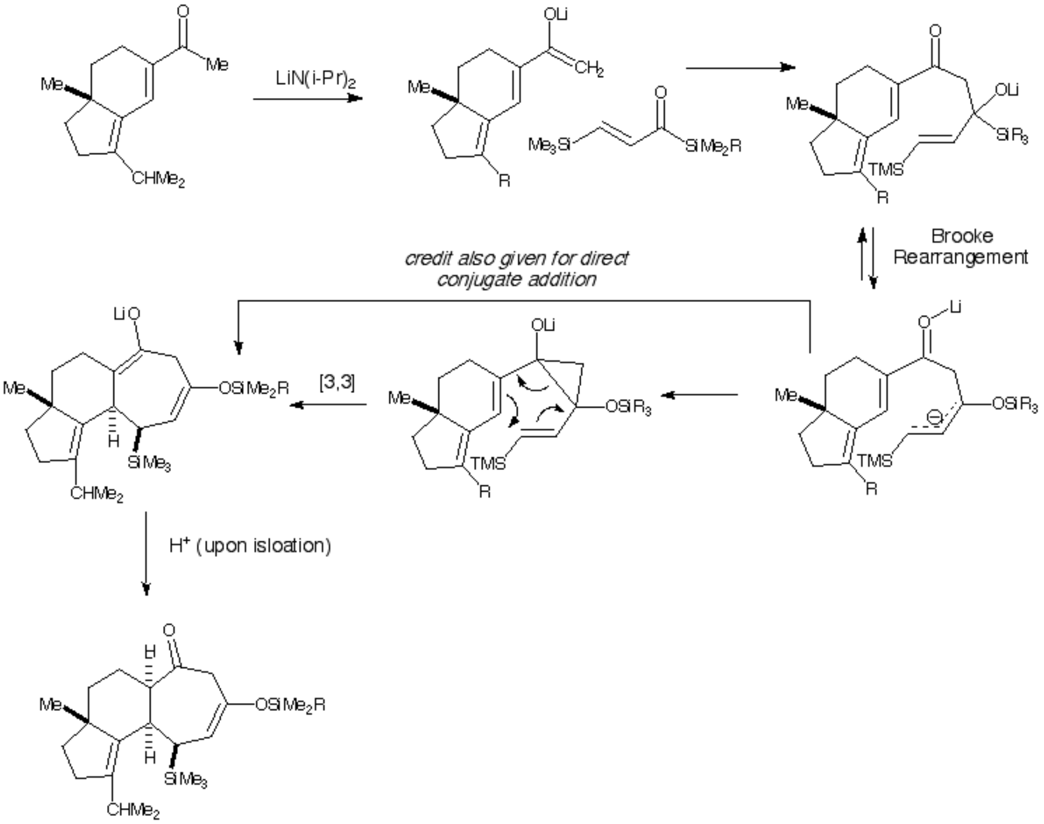
## Problem 10

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2000**, *2*, 1903

Takeda and co-workers have recently reported the mechanistically interesting ring extension reaction illustrated below (*Org. Lett.* **2000**, 2, 1903).

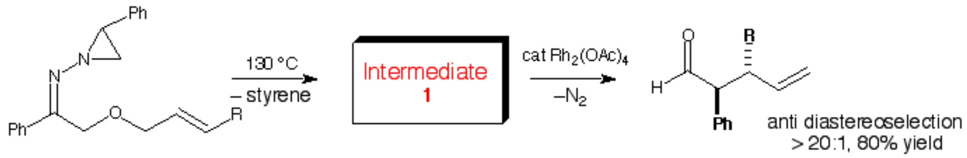


Provide a plausible mechanism for this transformation in the space below.
*Ignore the stereochemical aspect of this transformation.*



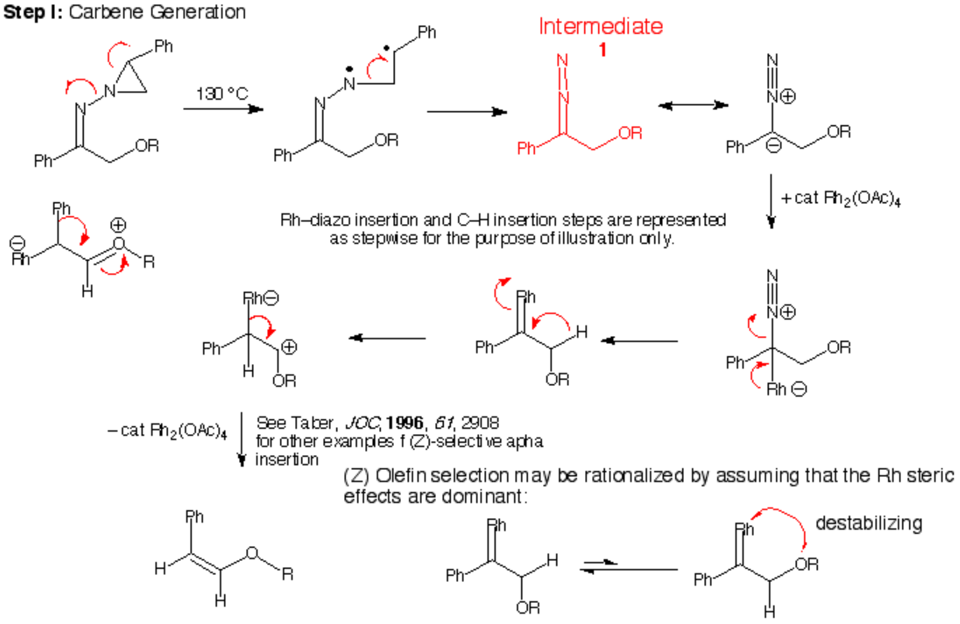
**Problem 13** Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2002**, *124*, 12426

The following transformation was recently reported by Stoltz (*J. Am. Chem. Soc* **2002**, *124*, 12426). In addition to the illustrated product, styrene and dinitrogen are produced as by-products in this transformation.



Provide a plausible mechanism for this transformation in the space below and identify intermediate **1**. Your mechanism should provide a rationalization for the product stereochemical relationship.

**Step I:** Carbene Generation

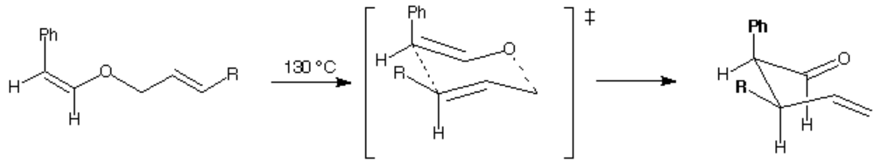


Rh–diazo insertion and C–H insertion steps are represented as stepwise for the purpose of illustration only.

See Taber, *JOC*, **1996**, *61*, 2908 for other examples f (Z)-selective apha insertion

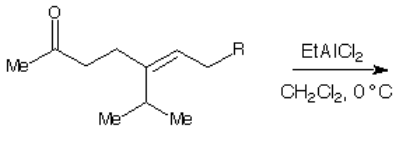
(Z) Olefin selection may be rationalized by assuming that the Rh steric effects are dominant:

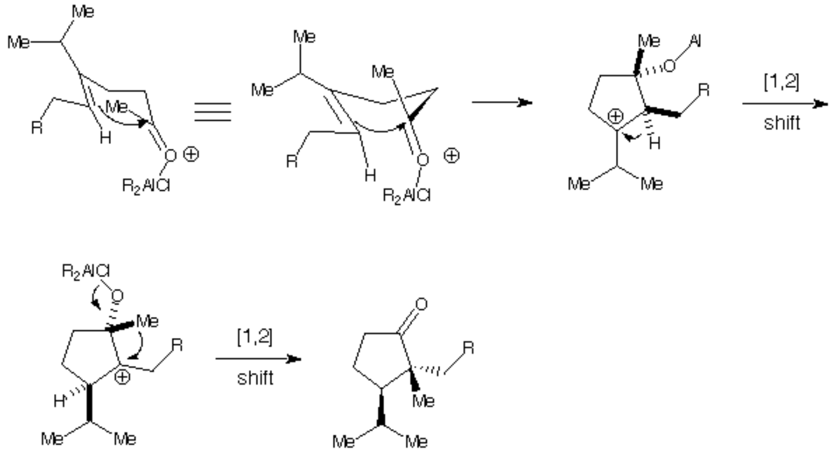
**Step II:** Claisen Rearrangement



**Problem 17** Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2001**, *3*, 569-572

The reaction illustrated below was recently reported by Snider and co-workers (Org. Lett. **2001**, *123*, 569-572). Provide a mechanism for this transformation in the space below. Where stereochemical issues are present, provide clear three dimensional drawings to support your answer.

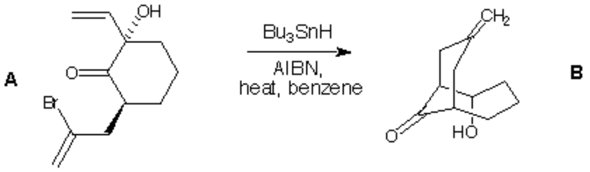




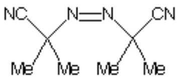
## Problem 18

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2001**, *3*, 1181-1183

The following transformation was recently reported by Rodriguez (*Org. Lett.* **2001**, *3*, 1181-1183).

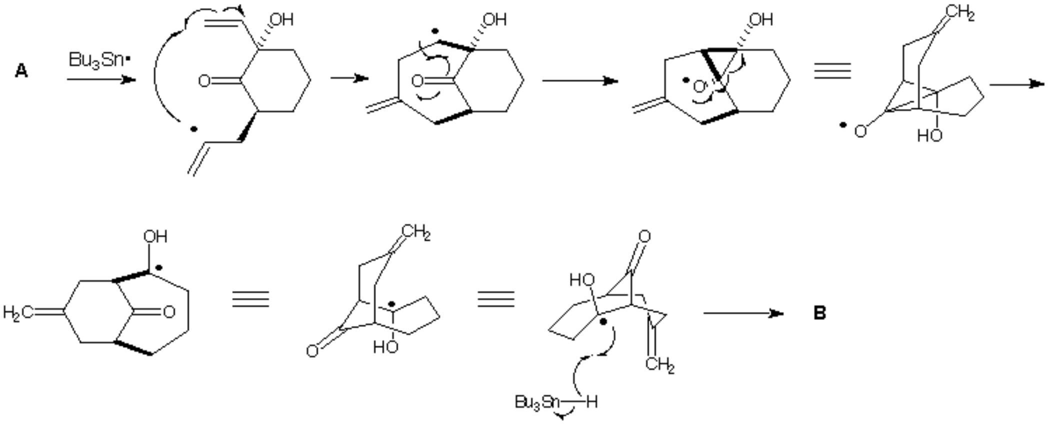


**Part A** What is the structure and function of AIBN in this reaction?



AIBN functions as a radical initiator

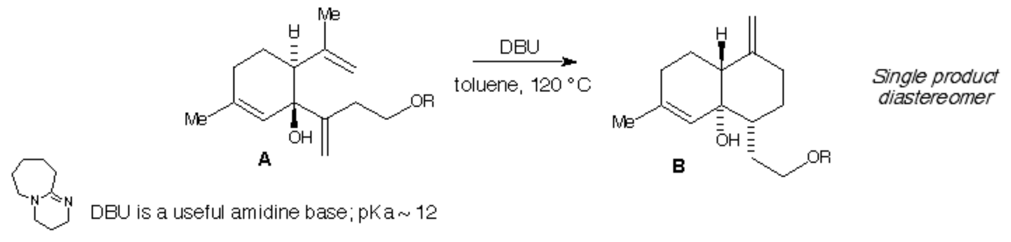
**Part B** Provide a mechanism for the illustrated rearrangement(s) of **A** to **B**. Where stereochemical issues are present, provide clear three dimensional drawings to support your answer.



## Problem 19

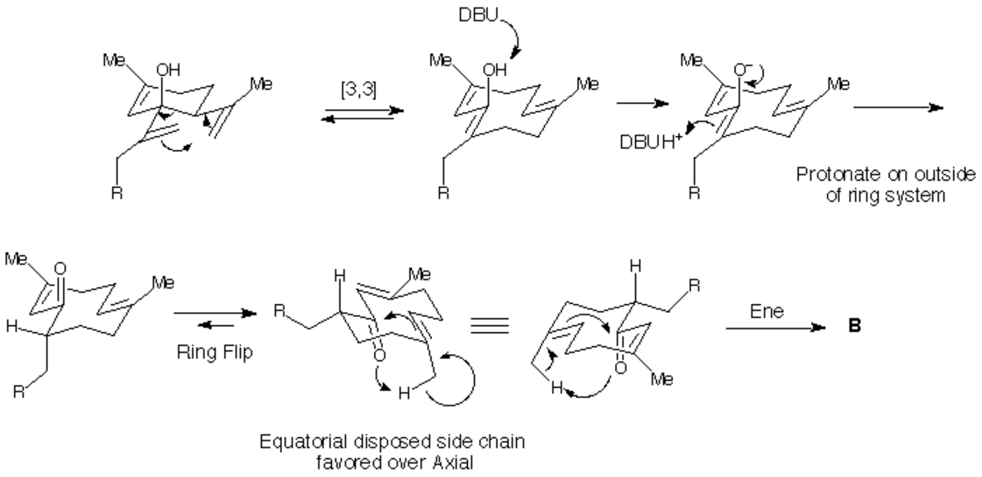
Contributer: **David A. Evans**
Citation: *Organic Lett.* **2001**, *3*, 1925-1927

The following transformation was recently reported by Barriault and Deon in conjunction with their synthesis of arteanniun M (*Org. Lett.* **2001**, *3*, 1925-1927). Provide a mechanism for the illustrated thermal rearrangement(s) of **A** to **B**. Where stereochemical issues are at stake, provide clear three dimensional drawings to support your answer.



Me
H
Me
OH
OR
A
DBU
toluene, 120 °C
H
Me
OH
OR
B
Single product diastereomer
DBU is a useful amidine base; pKa ~ 12

Provide your answer in the space below:



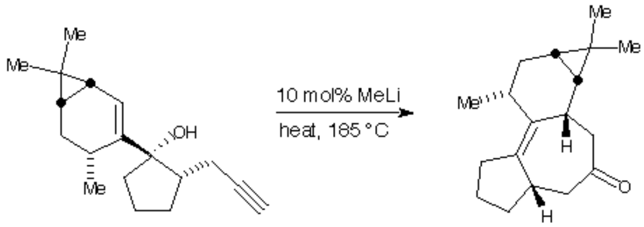
Me
OH
Me
R
[3,3]
DBU
Me
OH
Me
R
Me
O⁻
Me
DBUH⁺
R
Protonate on outside of ring system
Me
O
Me
H
R
Ring Flip
H
Me
R
O
H
Equatorial disposed side chain favored over Axial
H
R
O
Me
H
Ene
B

**Problem 20**

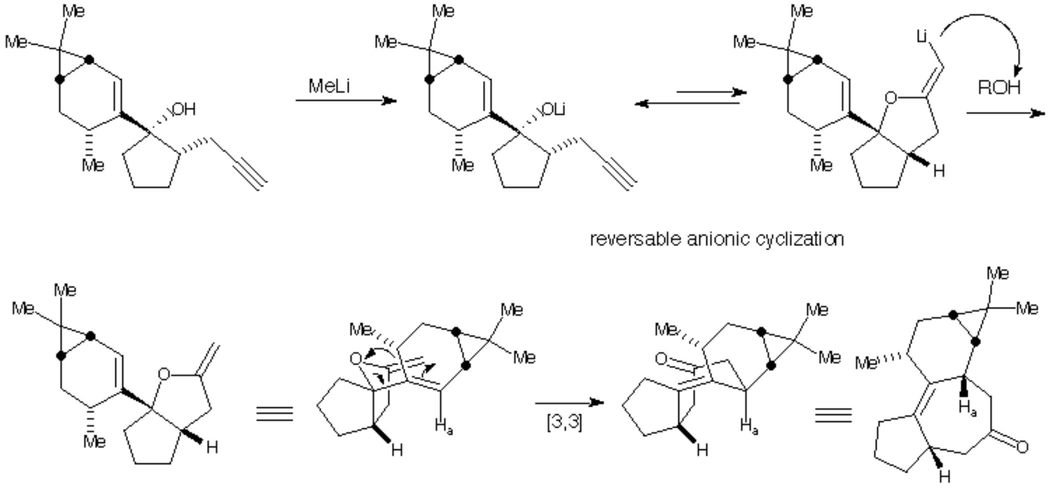
Contributer: **David A. Evans**

Citation: *Organic Lett.* **2001**, *3*, 115-117

T. V. Ovaska and co-workers have recently reported the complex rearrangement illustrated below as an entry into the phorbol skeleton (*Org. Lett* **2001**, *3*, 115-117). Provide a mechanism for the illustrated transformation. Where stereochemical features are an issue, provide clear three dimensional drawings to support your answer.



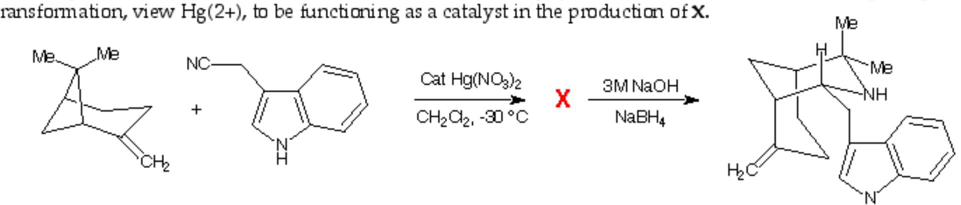
Provide your answer in the space below:



## Problem 22

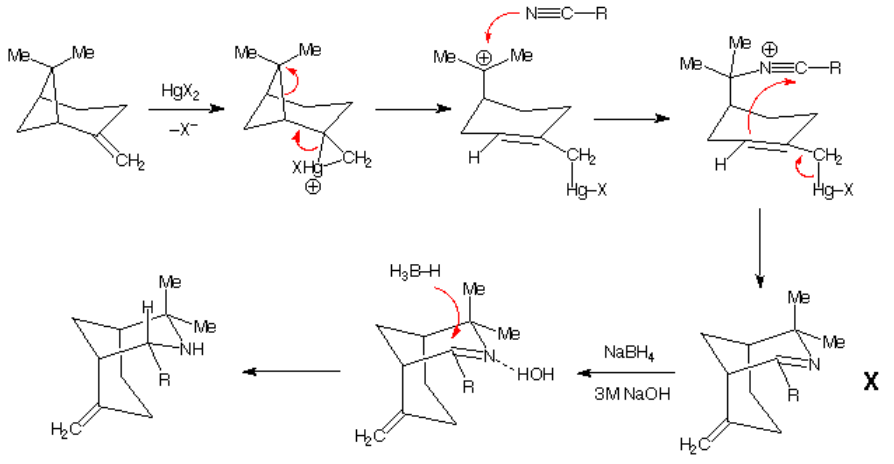
Contributer: **David A. Evans**
Citation: *Chem. Commun.* **1983**, 384

An interesting example of the **Ritter Reaction** was reported some time ago by R. V. Stevens (*Chem. Comm.* 384 **1983**). The relevant process illustrated below afforded an efficient two-step synthesis of makomakine. In contemplating this transformation, view Hg(2+), to be functioning as a catalyst in the production of **X**.



makomakine

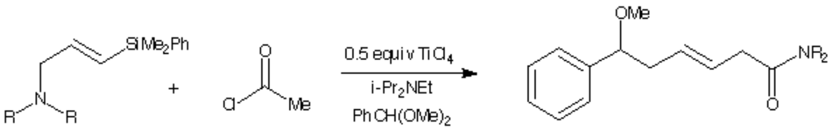
In the space below, provide a mechanism for the illustrated two-step transformation and identify the structure **X**.



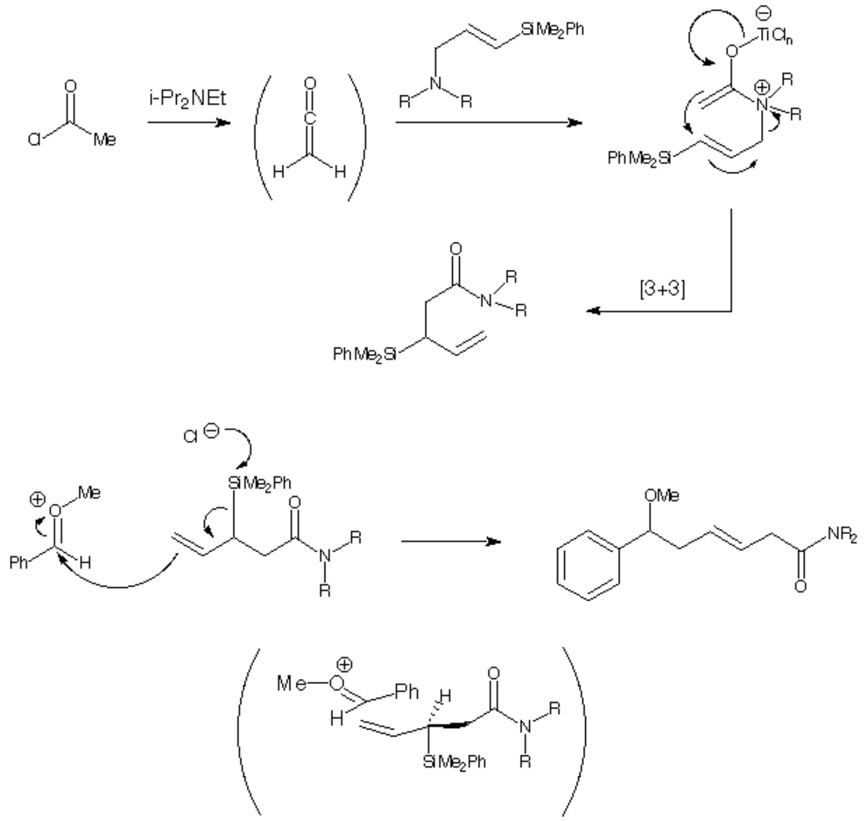
## Problem 31

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1999**, *121*, 9726

In the Panek lecture he described the transformation illustrated below. This transformation is an extrapolation of the recent publication of MacMillan and co-workers (*JACS*, **1999**, *121*, 9726).



Provide a detailed mechanism for the illustrated transformation. Use three-dimensional representations, where relevant, to illustrate the stereochemical aspects of the individual steps.

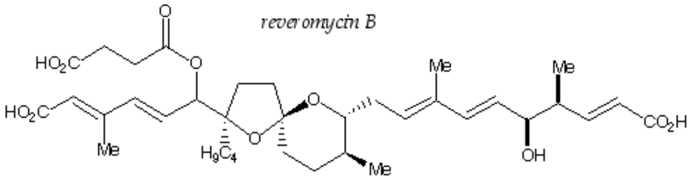


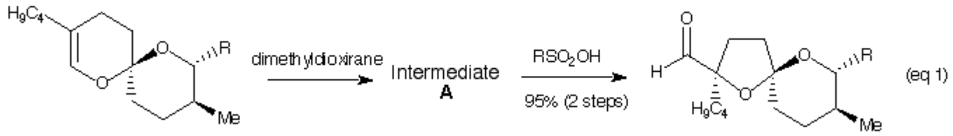
Alignment of crotylsilane necessary for *trans* olefin geometry

## Problem 33

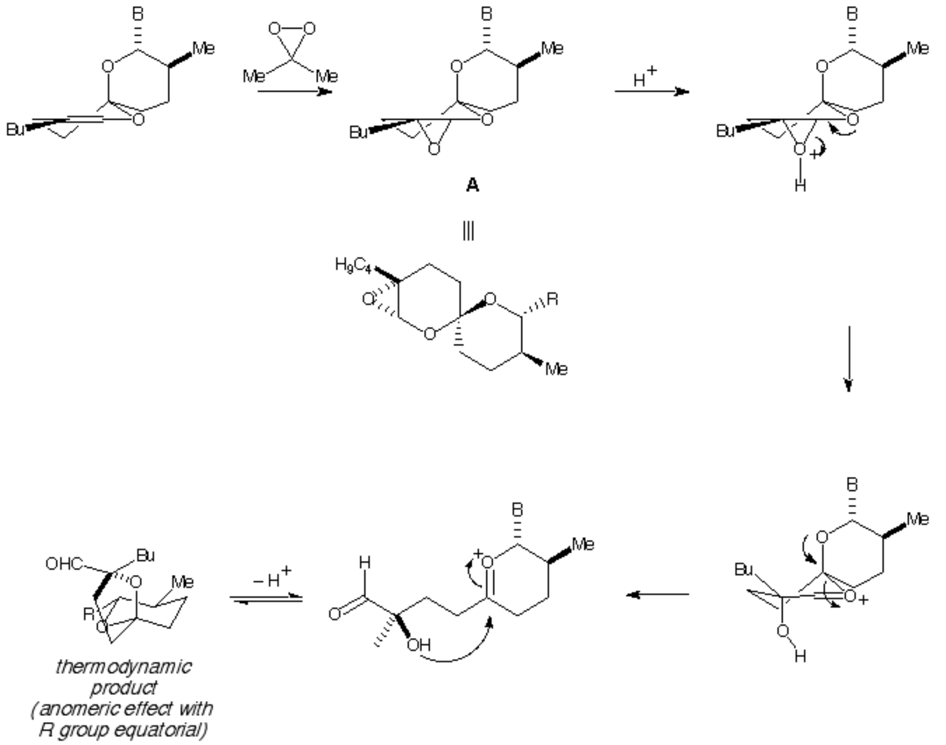
| | |
|---|---|
| Contributer: | **David A. Evans** |
| Citation: | *Organic Lett.* **2000**, *2*, 191 |

Recently, Rizacassa reported the synthesis of the spiroketal-containing natural product reveromycin B. An important transformation in this synthesis was the rearrangement illustrated below (eq 1) (Rizacassa *Org. Letters.* **2000**, *2*, 191).





Provide a mechanism for the overall transformation in the space below. It is important that you deduce the stereochemistry of intermediate **A**. Use three-dimensional representations, where relevant, to illustrate the stereochemical aspects of the individual steps.


B
Me
O
Bu
O
O–O
Me
Me
A
H+
H
|||
H9C4
O
O
O
R
Me
–H+
OHC
Bu
R
Me
H
O
OH
+
thermodynamic product (anomeric effect with R group equatorial)

## Problem 36

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1998**, *39*, 2247-2248

Consult the cited reference for an answer to this question

## Problem 38

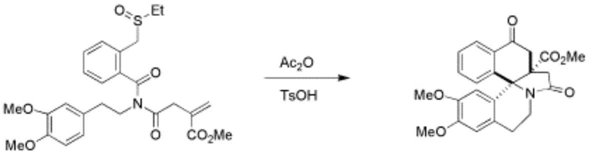
Contributer: **David A. Evans**
Citation: *Helv. Chem. Acta* **1997**, *80*, 2148-2156

Consult the cited reference for an answer to this question

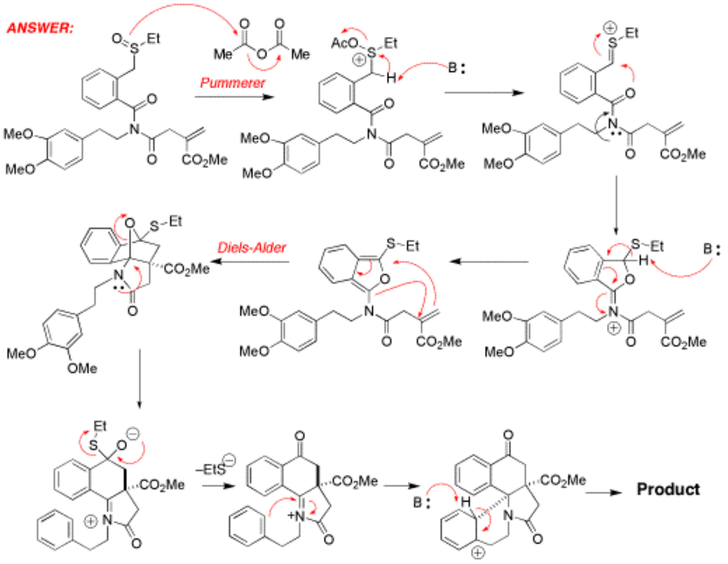
## Problem 41

Contributer: **Robert M. Williams**
Citation: *Tetrahedron Lett.* **1995**, *36*, 3495-3498

Padwa reported the interesting transformation shown below. Provide a detailed mechanism and identify any organic named reactions in this sequence. (Padwa, A. *Tet. Lett.*, **1995**, *36*(20), 3495-3498)

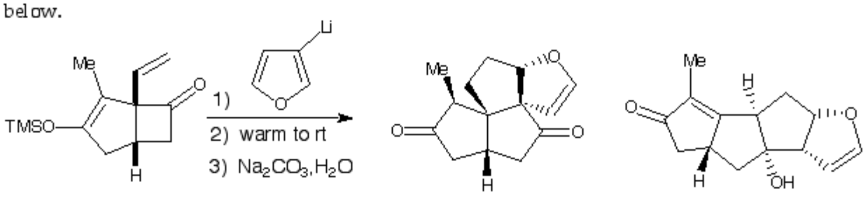


**ANSWER:**



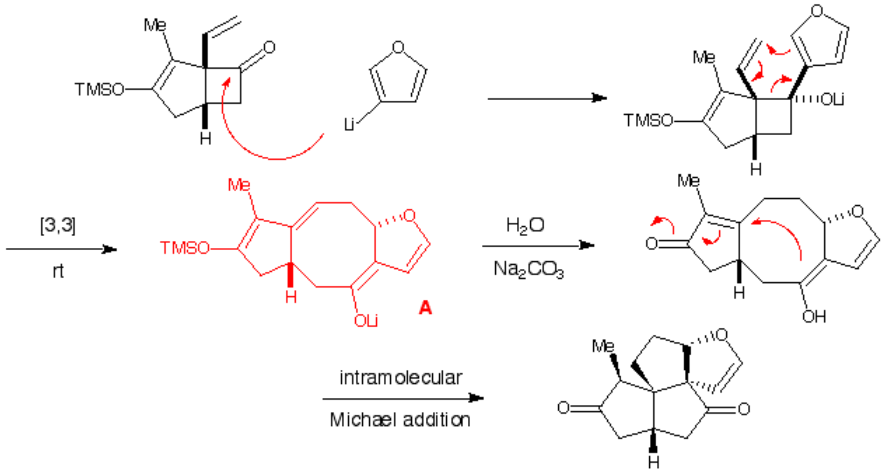
**Problem 43** Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1996**, *61*, 7976

Moore (*J. Org. Chem.* **1996**, *61*, 7976) recently reported the elegant 3-step transformation that is illustrated by the specific example below.

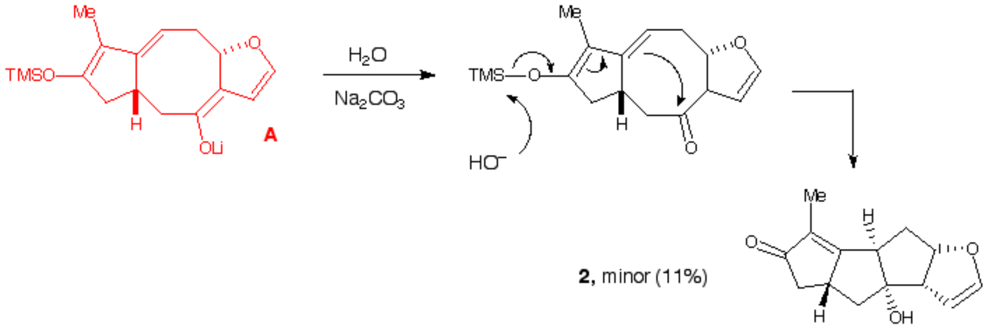


**1,** major (57%) **2,** minor (11%)

**Part A.** Draw out a plausible mechanism for the transformation to the major product isomer **1.**



**Part B.** Draw out a plausible mechanism for the transformation to the minor product isomer **2.**

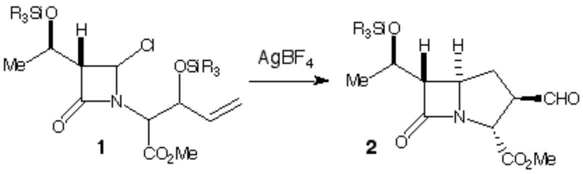


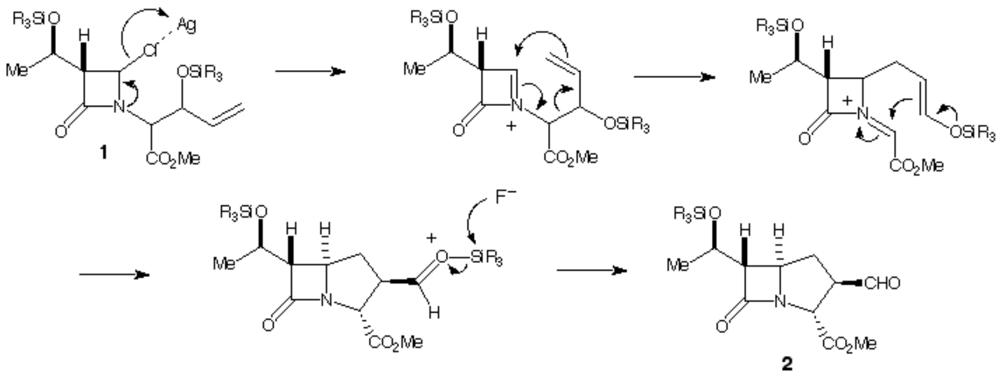
## **Problem 46**

Contributer: **David A. Evans**
Citation: *Chem. Commun.* **1995**, 2527

Sakurai (*Chem. Commun.* **1995**, 2527) recently reported the silver ion induced rearrangement of **1** to the bicyclic β-lactam **2**.

Provide a plausible mechanism for this transformation in the space below.



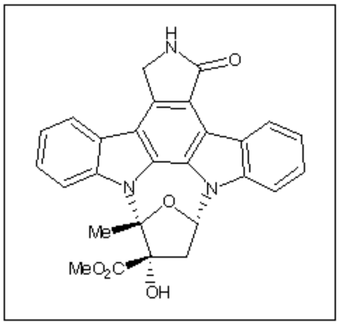


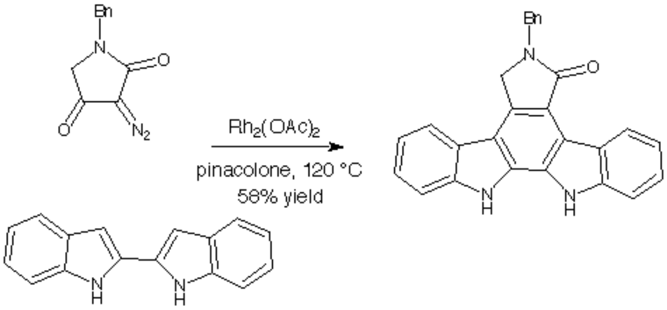
an aza-Prins–pinacol rearrangement could also be a plausible mechanism

## Problem 47

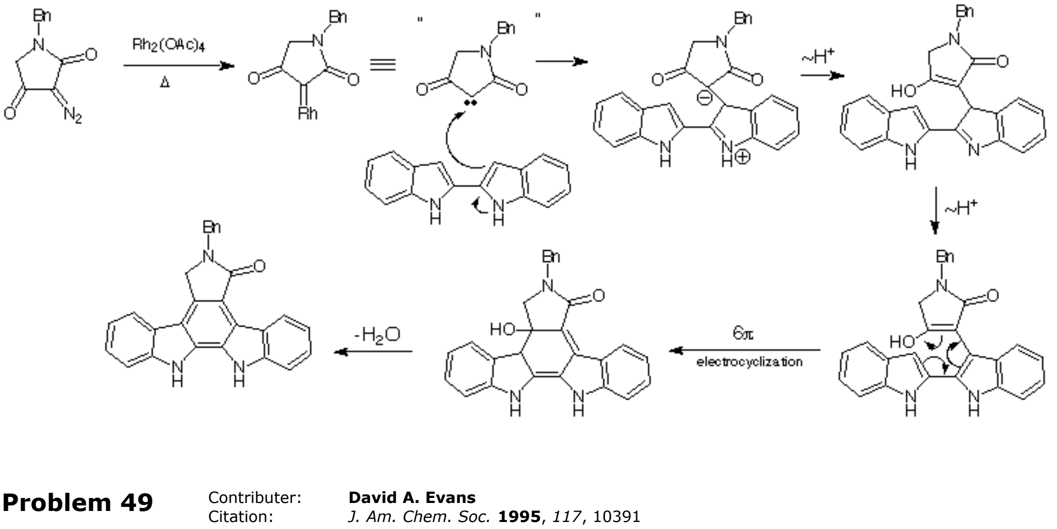
Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1995**, *117*, 10413

Wood recently reported a very clever approach to the synthesis of the indolocarbazole family of natural products (*JACS* **1995**, *117*, 10413). His approach to the indolocarbazole core is the one-pot transformation outlined below.





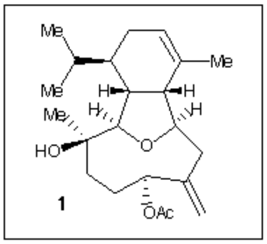
Provide a plausible mechanism for this multi-step transformation in the space below.



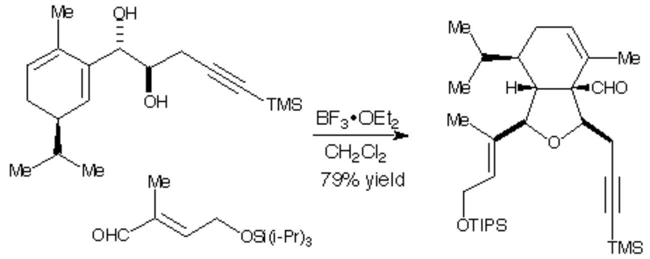
## Problem 49

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1995**, *117*, 10391

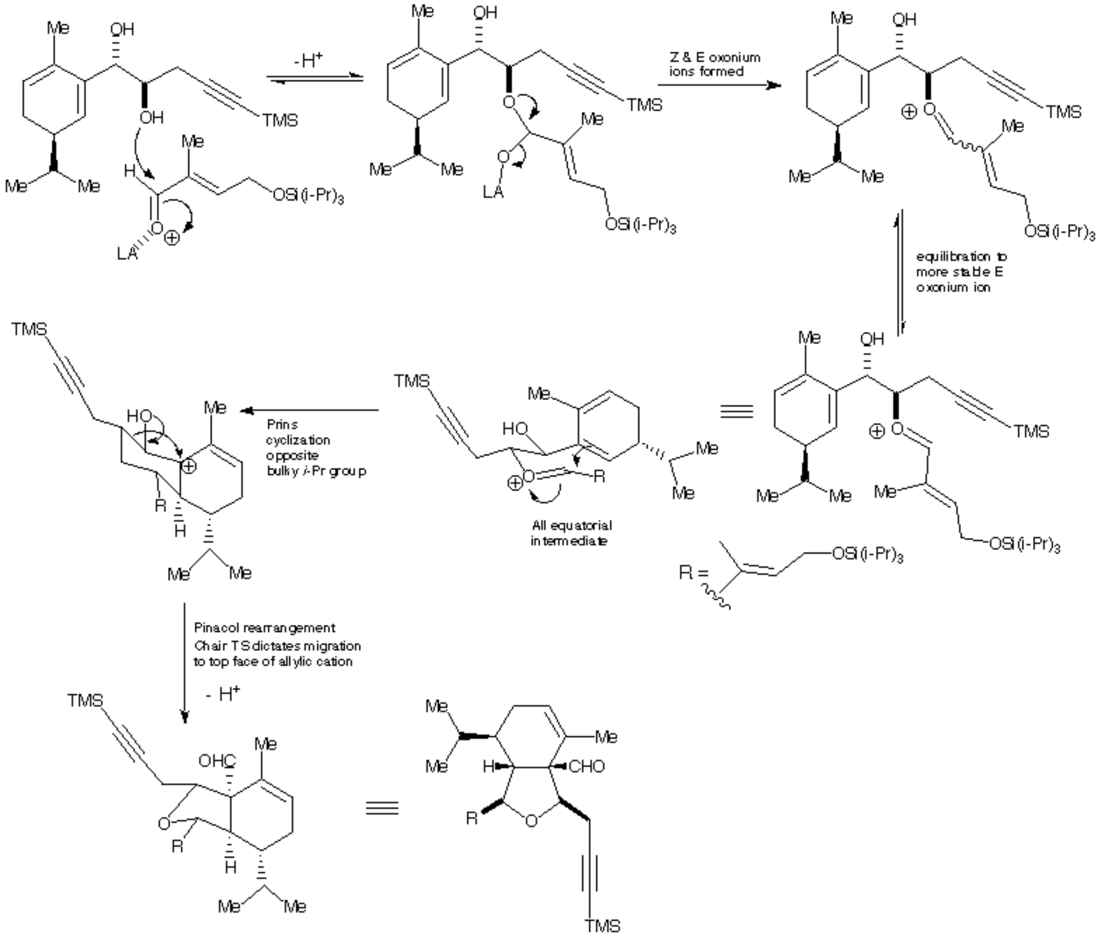
Overman and MacMillan (*JACS* **1995**, *117*, 10391) recently reported the synthesis of the diterpene, 7-deacetoxyalcyonin (**1**) illustrated below. The keynote reaction in this synthesis is the Lewis acid catalyzed transformation illustrated below, a process that has previously been investigated in the Overman Group (*JACS* **1991**, *113*, 3534).



**1**

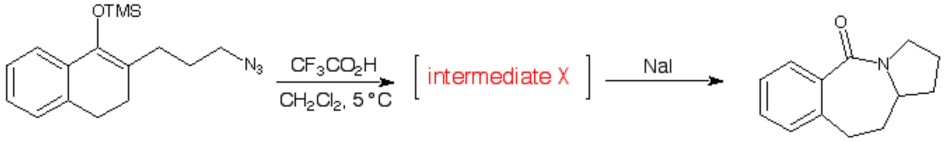


Propose a detailed mechanism for this transformation. Be sure to clearly identify the stereochemical control elements that are operating in the creation of the new stereogenic centers.


-H+
Z & E oxonium ions formed
LA
OSi(i-Pr)3
TMS
equilibration to more stable E oxonium ion
Prins cyclization opposite bulky i-Pr group
All equatorial intermediate
R =
Pinacol rearrangement
Chair TS dictates migration to top face of allylic cation
- H+
OHC
CHO
R
TMS

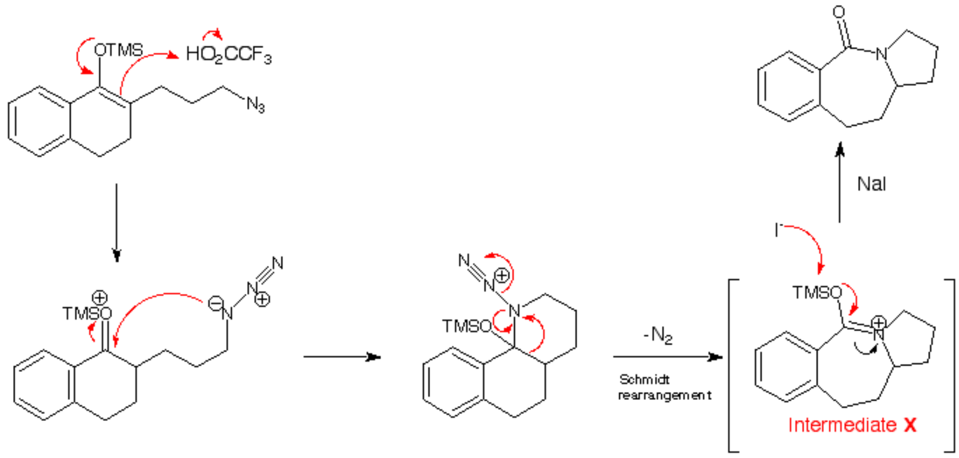
**Problem 51** Contributer: **David A. Evans**
Citation: *Tetrahedron* **1996**, *52*, 3403

Aube (*Tetrahedron* **1996**, 52, 3403) recently reported an efficient approach to the synthesis of polycyclic lactams. A typical transformation is provided below (eq 2).



(2)

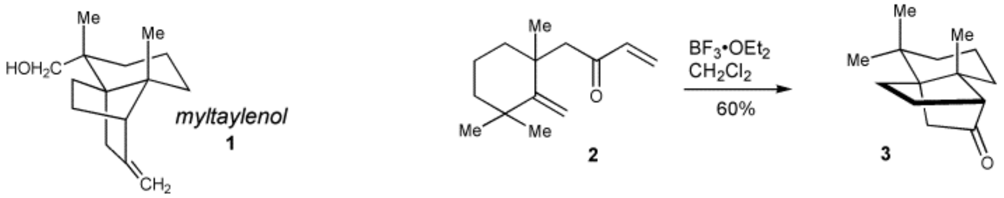
Provide a plausible mechanism for this transformation in the space below.



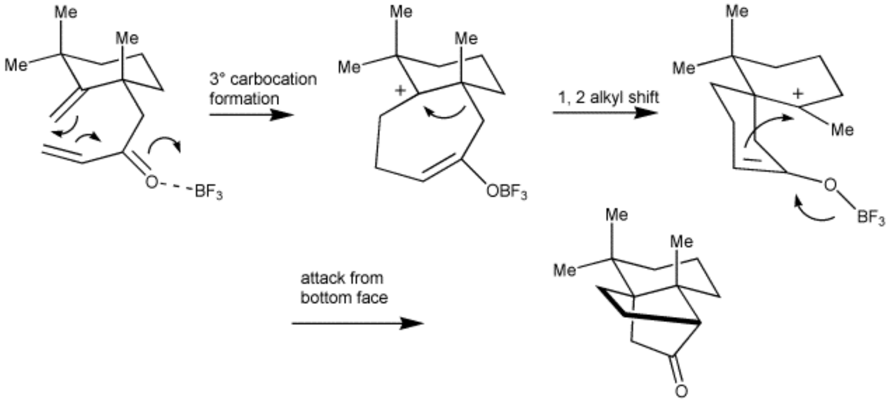
## Problem 56

Contributer: **Grace Wang**
Citation: *Chem. Commun.* **1994**, 2259

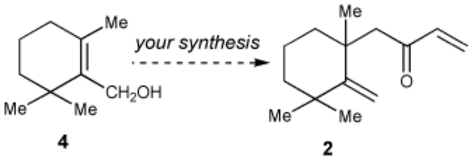
The recently isolated irregular sesquiterpene myltaylenol (**1**) stimulated Srikrishna and co-workers (*Chem Commun*. **1994**, 2259) to study the biogenetically modeled acid-promoted rearrangement of **2** which leads to the desired terpenoid skeleton in good yield. In the space below provide a detailed mechanism for the transformation of **2** to **3**.

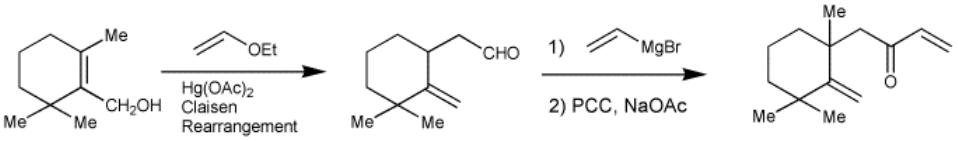


**Part A.** Provide a mechanism for the transformation of **2** to **3**.



**Part B.** Provide an expedient synthesis of **2** from the allylic alcohol **4**.





## Problem 57

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1993**, *34*, 579

Consult the cited reference for an answer to this question

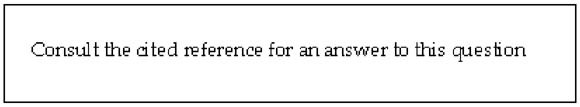
## Problem 60

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1987**, *28*, 1267

Consult the cited reference for an answer to this question

## Problem 72

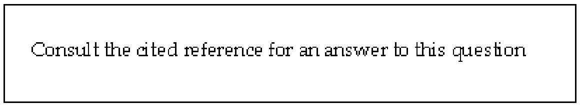
Contributer: **David A. Evans**
Citation: *Angew. Chem.* **2002**, *41*, 4316



Consult the cited reference for an answer to this question

## Problem 73

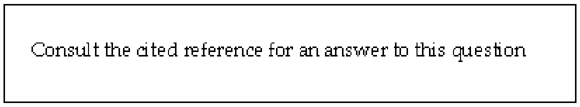
Contributer: **David A. Evans**
Citation:



Consult the cited reference for an answer to this question

## Problem 78

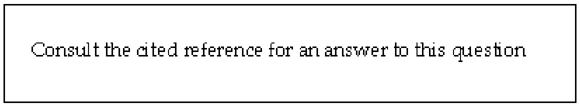
Contributer: **David A. Evans**
Citation: *Chem. Commun.* **2003**, 276



Consult the cited reference for an answer to this question

## Problem 79

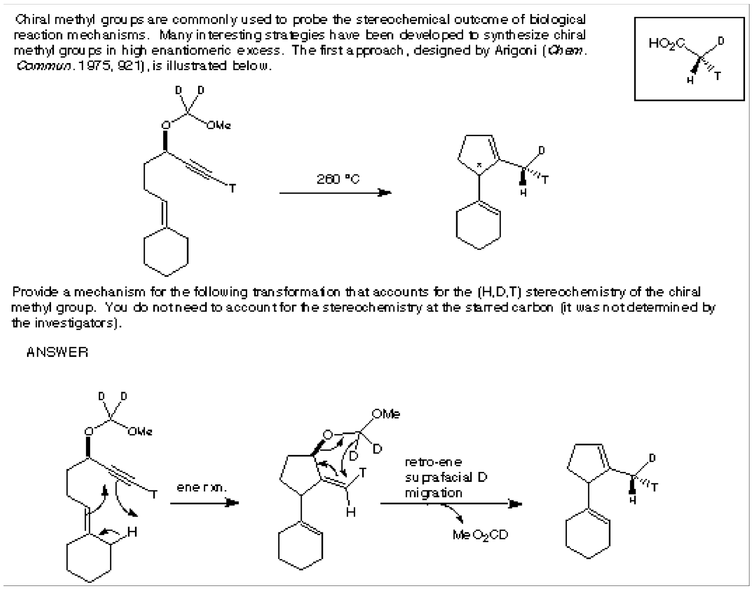
Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1988**, *110*, 6558



Consult the cited reference for an answer to this question

## Problem 82

Contributer: **David A. Evans**
Citation: *Chem. Commun.* **1975**, 921



Chiral methyl groups are commonly used to probe the stereochemical outcome of biological reaction mechanisms. Many interesting strategies have been developed to synthesize chiral methyl groups in high enantiomeric excess. The first approach, designed by Arigoni (*Chem. Commun.* 1975, 921), is illustrated below.

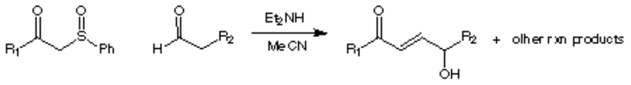
Provide a mechanism for the following transformation that accounts for the (H,D,T) stereochemistry of the chiral methyl group. You do not need to account for the stereochemistry at the starred carbon (it was not determined by the investigators).

ANSWER

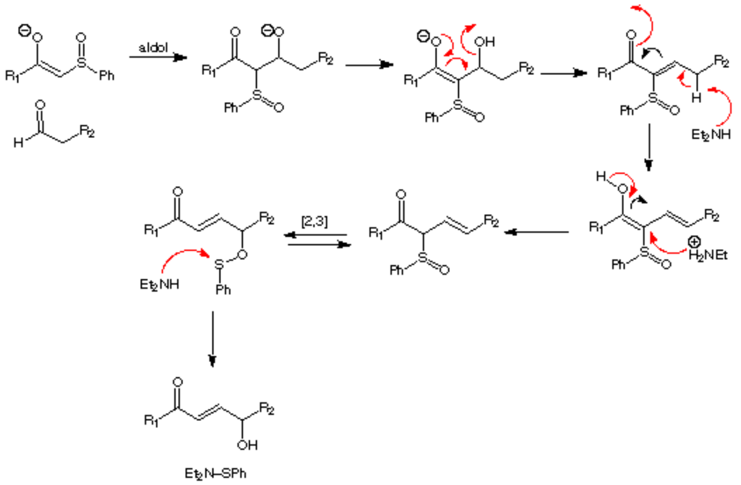
## Problem 83

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2001**, *66*, 1228

The illustrated Knovenagel-type condensation recently reported by Nokami et al. (*J. Org. Chem.* 2001, *66*, 1228) should prove to be a generally useful transformation.



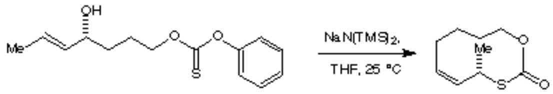
In the space below, provide a mechanism for the indicated transformation.



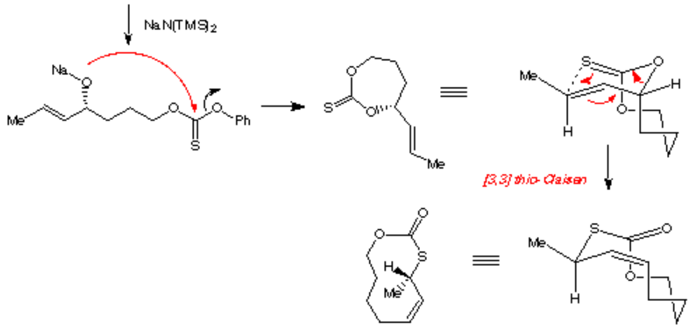
## Problem 84

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* , *31*, 5471

The illustrated transformation was reported by Kurihara et al. (*Tet. Lett.* 1990, *31*, 5471).



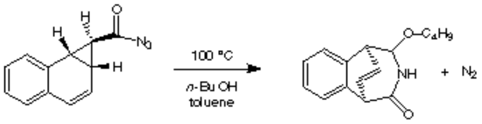
Provide a mechanism for the indicated transformation that accounts for the overall stereochemical outcome of the reaction. Three dimensional drawings should be provided to support your answer.



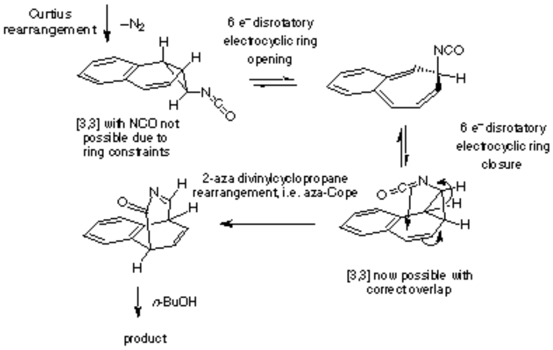
## Problem 85

Contributer: **David A. Evans**
Citation: *Tetrahedron* **1959**, *5*, 53

In a classic thermal transformation first disclosed by Doering and Goldstein (*Tetrahedron*, 1959, *5*, 53), the acyl azide below was heated in the presence of butanol to afford a 1:1 mixture of diastereomers. Later studies by Müller and coworkers determined that enantiomerically pure starting material provides enantiomerically pure lactam product.



Please provide a mechanism of this transformation while paying particular attention to the stereochemistry of the process.

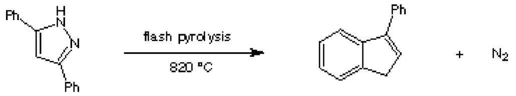


Curtius rearrangement
–N2
6 e⁻ disrotatory electrocyclic ring opening
NCO
H
H
H
H
N=C=O
[3,3] with NCO not possible due to ring constraints
6 e⁻ disrotatory electrocyclic ring closure
2-aza divinylcyclopropane rearrangement, i.e. aza-Cope
O=C=N
H
H
H
O
N
H
H
H
[3,3] now possible with correct overlap
n-BuOH
product

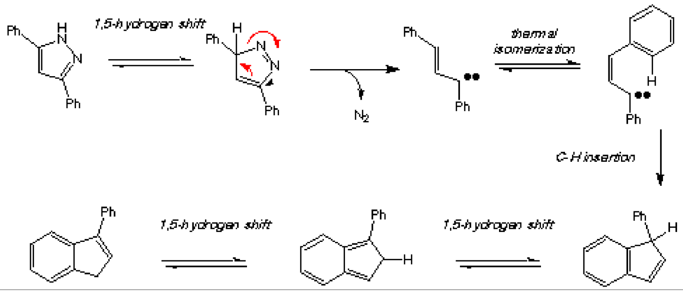
## Problem 88

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1998**, *63*, 8188

Please provide a mechanism for the following high temperature reaction that was reported by Yranzo and co-workers (*J. Org. Chem.* 1998, *63*, 8188).



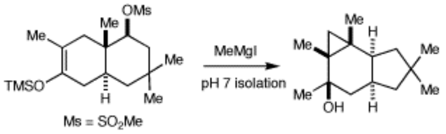
Draw a plausible mechanism for the transformation to the major product isomer. *Do not invoke any radical intermediates in your answer.*

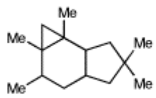


## Problem 90

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2001**, *66*, 2350

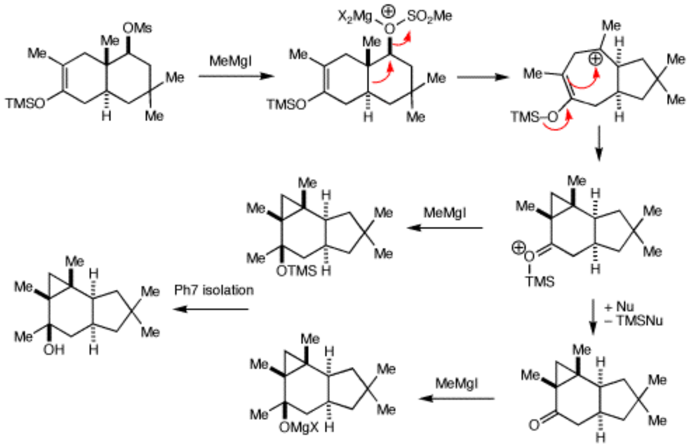
The synthesis of the marasmane sesquiterpene skeleton has been to topic of several research groups. In a recent paper (*J. Org. Chem.* **2001**, *66*, 2350) de Groot et al. have developed an ingeneous approach to the assemblage of this ring system.





marasmane skeleton

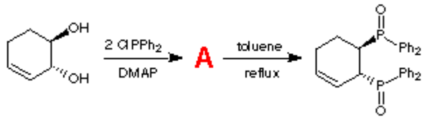
In the space below, provide a mechanism for the indicated transformation.



## Problem 96

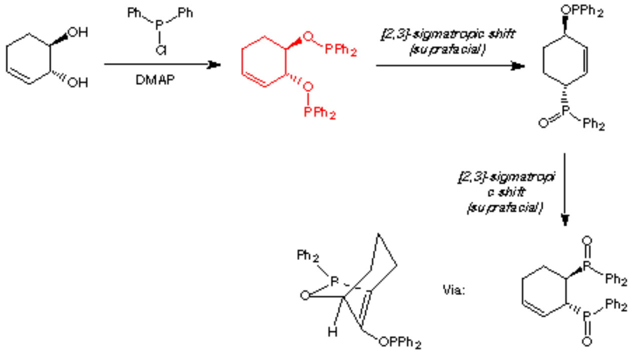
Contributer: **David A. Evans**
Citation: *Angew. Chem.* **2001**, *40*, 1235

Frequently, the limiting factor in the widespread use of chiral catalysts is the efficiency of the chiral ligand synthesis. Knochel (*Angew. Chem. Int. Ed.* 2001, *40*, 1235) has developed an efficient rhodium catalyst for asymmetric Hydroboration. The key step in the synthesis of the chiral ligand is illustrated below (eq 1).



(1)

Please provide a mechanism for the reaction in equation 1 and identify the intermediate A.



## Problem 103

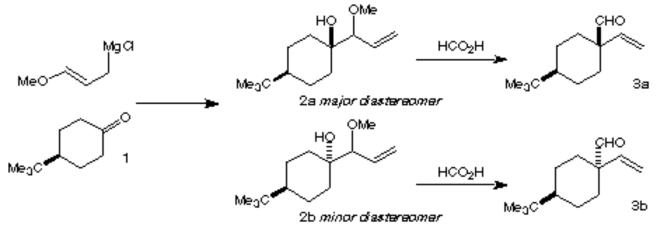
Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **2003**, *44*, 1129-1132

Consult the cited reference for an answer to this question

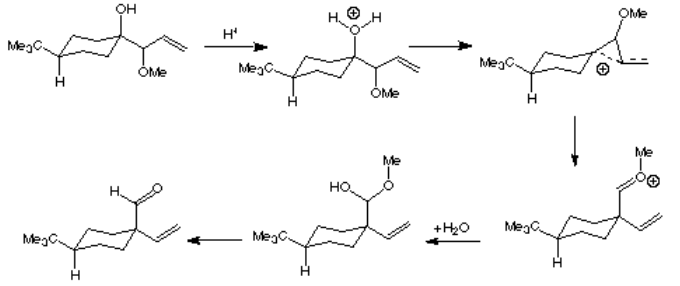
## Problem 104

Contributer: **David A. Evans**
Citation: *Evans, Unpublished Results*

The indicated allylmetal nucleophile adds regioselectively to the indicated cyclohexanone derivative 1 to afford the tertiary alcohols 2a and 2b having the indicated stereochemistry (Evans & Andrews, *Unpublished*, 1974). These adducts may be individually rearranged to the indicated aldehydes 3a and 3b with complete control of stereochemistry. This set of transformations readily provides access to functionalized quaternary centers.



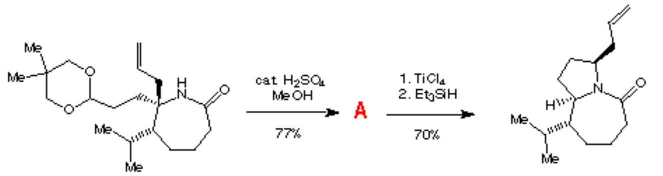
Provide a mechanism for the transformation of 2a into 3a that is consistent with the experimental observations. Where appropriate, provide three-dimensional drawings to reinforce your answer.



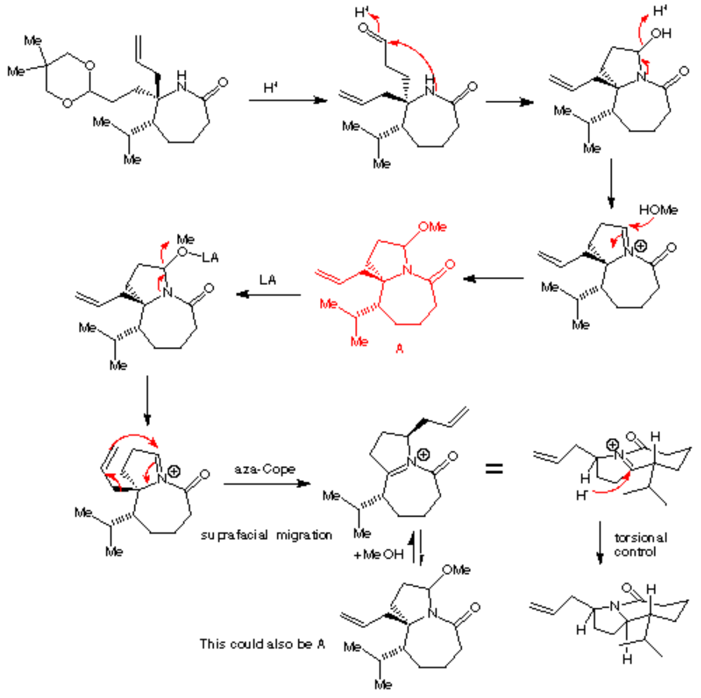
## Problem 107

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2001**, *66*, 7751

In Heathcock's recent synthetic approach to the *Stemona* alkaloids, an interesting series of transformations were used (Heathcock, JOC, 2001, 66, 7751).



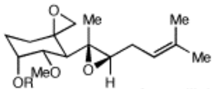
Please provide a mechanism for each reaction and identify the structure of intermediate A.



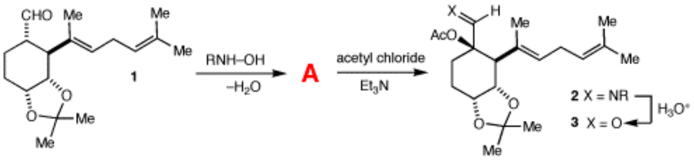
## Problem 108

Contributer: **David A. Evans**
Citation: *Angew. Chem.* **1999**, *38*, 971

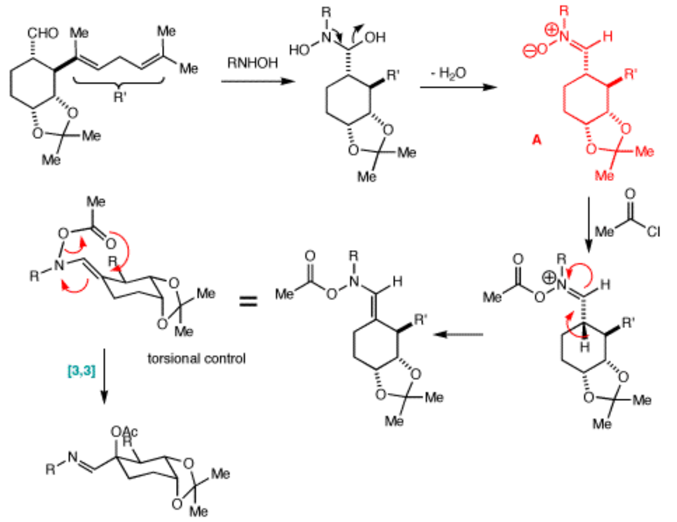
The fumagillin natural products possess several interesting biological properties including antibiotic activity against *Staphylococcus auereus*. In Sorensen's recent synthesis of fumagillol (*Angew. Chem, Int. Ed.* **1999**, *38*, 971), intermediate **1** was transformed into its a-oxygenated counterpart **3** through the indicated reaction sequence.



*fumagillol*

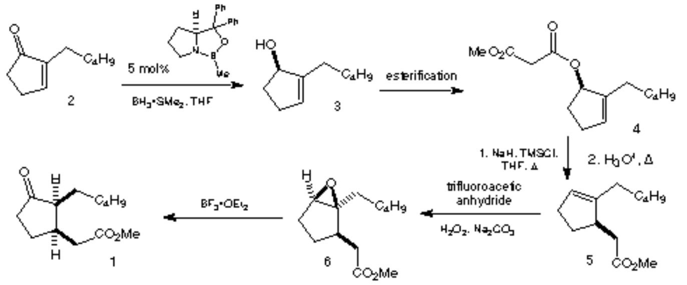


In the space below, identify the structure of intermediate **A** and provide a mechanism for the transformation of **1** into **2**.

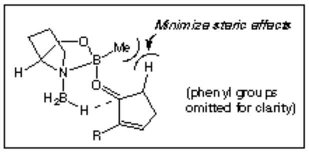


**Problem 116** Contributer: **David A. Evans**
Citation: *Angew. Chem.* **2000**, *39*, 569-573

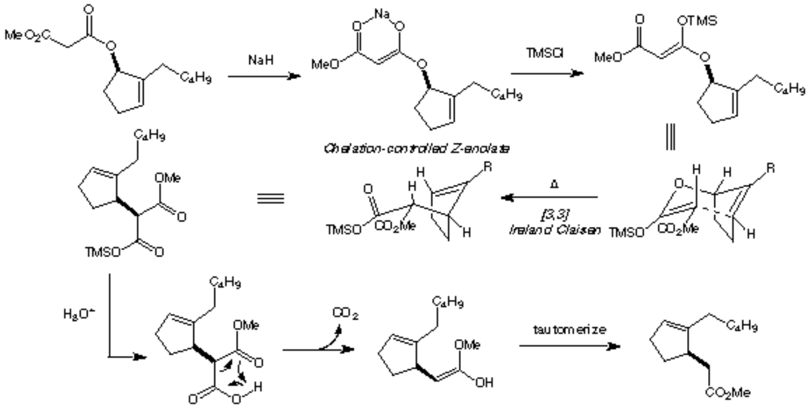
In their total synthesis of (+)-methyl epijasmonate (1), Fehr and co-workers (*Angew. Chem Int. Ed.* 2000, *39*, 569-573) deftly relay stereochemical relationships about the cyclopentane skeleton. Their synthetic sequence is outlined below.



Part A. Provide a clear 3-dimensional drawing which clearly illustrates the control elements for the reduction of 2 to 3.


*Minimize steric effects*
(phenyl groups omitted for clarity)

Part B. Provide a mechanism for the transformation of malonate 4 to methyl ester 5.



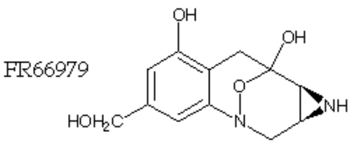
Part C. Discuss the stereochemical attributes of the epoxidation of 5 to give 6. *Hint: It should be noted here that other epoxidizing agents such as MCPBA are far less stereoselective.*

**Problem 117** Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2001**, *123*, 2448

Consult the cited reference for an answer to this question

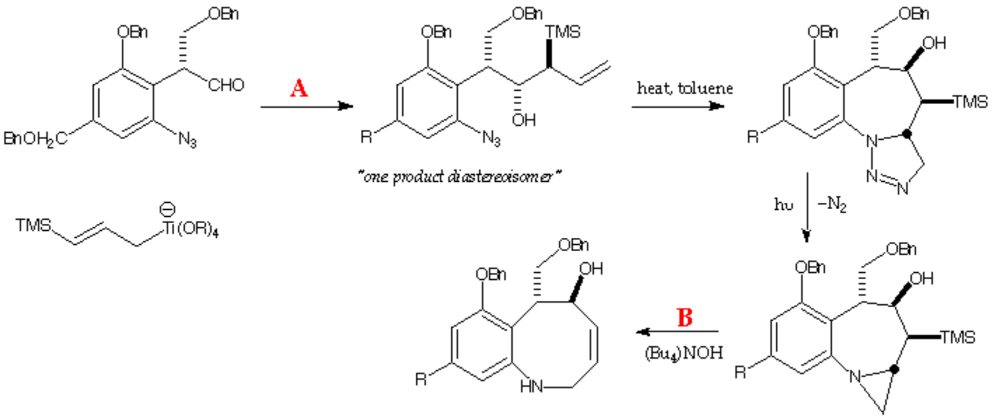
**Problem 118** Contributer: **David A. Evans**
Citation: *Angew. Chem.* **2002**, *41*, 4688

A stereoselective synthesis of the antitumor alkaloid FR66979 has been reported by Ciufolini (*Angew. Chem. Int. Ed.* **2002**, *41*, 4688). This question pertains to the transformations labeled **A** and **B**.

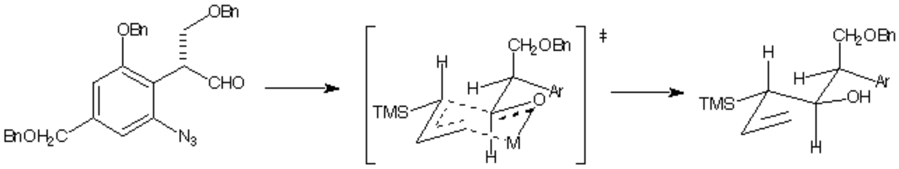


**Part A.** Rationalize the stereochemical outcome of this diastereoselective carbonyl addition.

**Part B.** Provide a deteiled mechanism for this transformation.



**Part A.** Rationalize the stereochemical outcome of this diastereoselective carbonyl addition.



**Part B.** Provide a deteiled mechanism for this transformation.

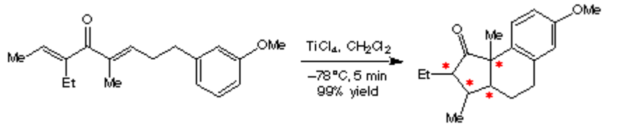
Consult the cited reference for a discussion of this transformation

**Problem 119** Contributer: **David A. Evans**
Citation: *Organic Lett.* **2002**, *4*, 1371

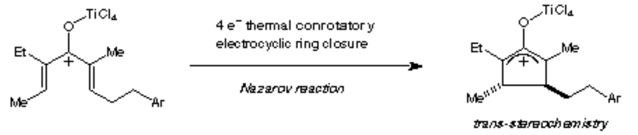
Consult the cited reference for an answer to this question

**Problem 122** Contributer: **David A. Evans**
Citation: *Organic Lett.* **2001**, *3*, 3033-3035

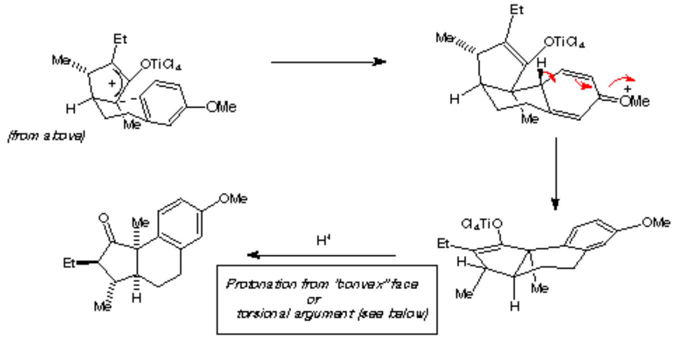
The interesting transformation illustrated below was recently reported by F. West and co-workers (*Org. Lett.* 2001, *3*, 3033-3035). The pivotal reaction upon which this transformation was designed is a pericyclic process that affords a pivotal element of stereocontrol.

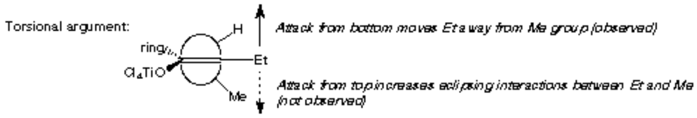


Part A. Identify the pericyclic process that intervenes in the illustrated transformation and illustrate the relative configuration(s) stereocenter(s) that are generated.



Part B. Provide a mechanism for the overall transformation. Since stereochemical issues are at stake, carefully rendered 3-D conformational drawings should be incorporated into your answer.

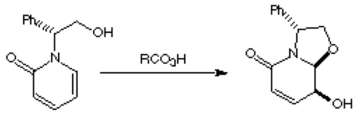


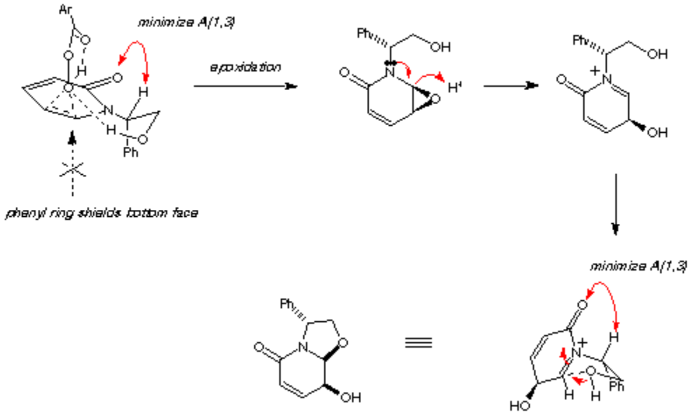

Torsional argument:
ring
$Cl_4TiO$
H
Et
Me
Attack from bottom moves Et away from Me group (observed)
Attack from top increases eclipsing interactions between Et and Me (not observed)

## Problem 125

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2001**, *3*, 3257-3260

The following reaction was recently reported by Amat and co-workers (*Org. Lett.* 2001, *3*, 3257-3260). Provide a mechanism for the this transformation which is consistent with the product stereochemistry. Since stereochemical issues are at stake, carefully rendered 3-D conformational drawings should be incorporated into your answer.

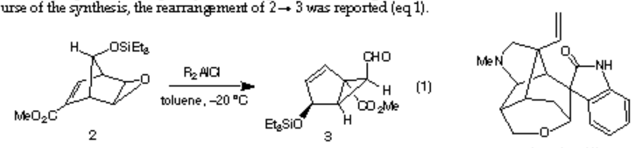




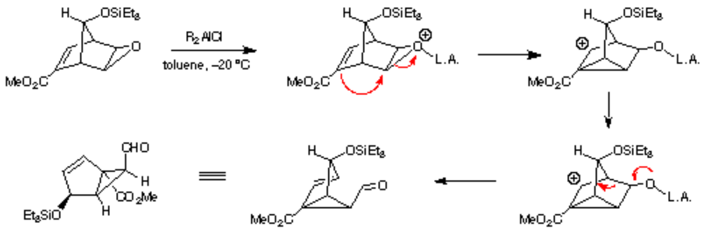
## Problem 139

Contributer: **David A. Evans**
Citation: *Angew. Chem.* **2000**, *39*, 4073

Fukuyama has recently reported an elegant synthesis of gelsamine (1) (*Angew. Chem. Int. Ed.* 2000, 39, 4073). During the course of the synthesis, the rearrangement of 2 → 3 was reported (eq 1).



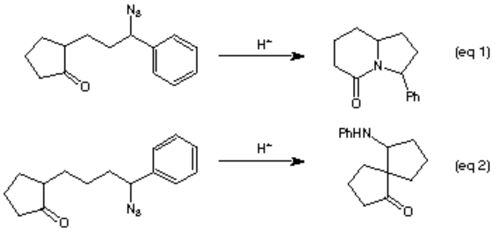
Provide a concise mechanism for this reaction in the space below.



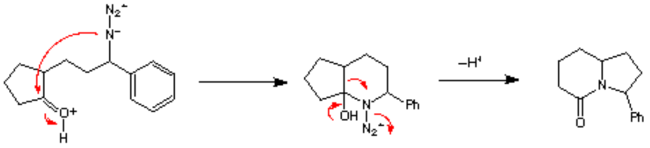
## Problem 141

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2001**, *66*, 886

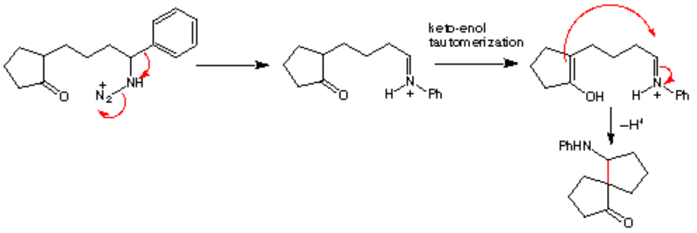
Aube has recently reported the transformations illustrated below (*J. Org. Chem.* 2001, 66, 886-889). In this study he has documented that the observed product is dependent on the tether length between the azide and carbonyl functional groups.



Part A. Provide a mechanism for the transformation illustrated in Eq 1.



Part B. Provide a mechanism for the transformation illustrated in Eq 2.



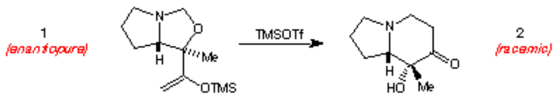
Part C. Briefly rationalize the difference in reactivity.

Cyclization of the azide onto the ketone in eq 1 forms a 6-membered ring and is therefore rapid. Cyclization of the azide onto the ketone in eq 2 would need to form a 7-membered ring, which is slow and allows the other reaction pathway to occur.

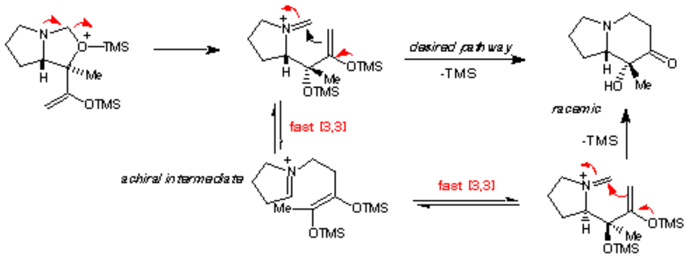
## Problem 142

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1992**, *57*, 1179

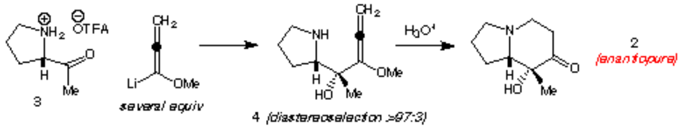
During the course of the Overman synthesis of pumilotoxin (*J. Org. Chem.* 1992, *57*, 1179) the indicated transformation was carried out with the expectation that the bicyclic ketone 2 would be enantiopure since the starting amine 1 was enantiomerically pure. Surprisingly, product 2 was obtained as a racemate.



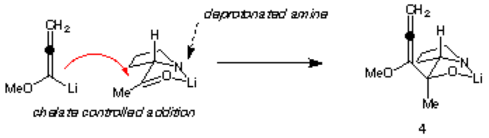
Part A. Provide a mechanism for this transformation that accounts for the illustrated stereochemical outcome.



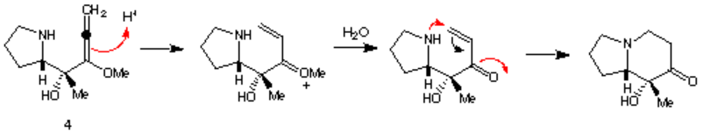
The revised synthesis of enantiomerically pure 2 is illustrated below (*J. Org. Chem.* 1992, *57*, 1179). Addition of 3 to several equivalents of the illustrated allenyllithium reagent afforded carbonyl adduct 4 as a single diastereomer. This intermediate was then transformed into enantiopure 2 under acidic conditions.



Part B. Provide an explanation for the high level of stereocontrol that is observed in the carbonyl addition step. A three dimensional drawing of the carbonyl addition transition state is requested in conjunction with this answer.

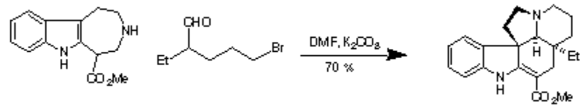


Part C. Provide a mechanism for the transformation of 4 to 2.

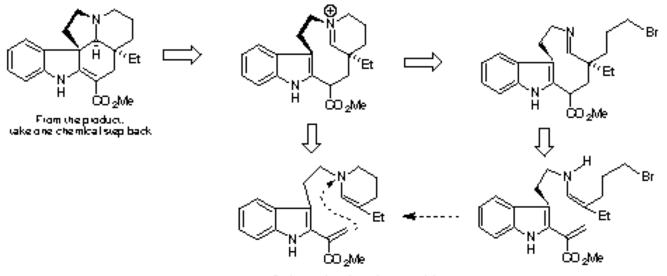


**Problem 145** Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1978**, *43*, 3705

Martin Kuhne has described a biomimetic approach to the construction of the aspidosperma alkaloid skeleton (*J. Org. Chem.* 1978, *43*, 3705). One of the reactions developed in his laboratory is illustrated below.



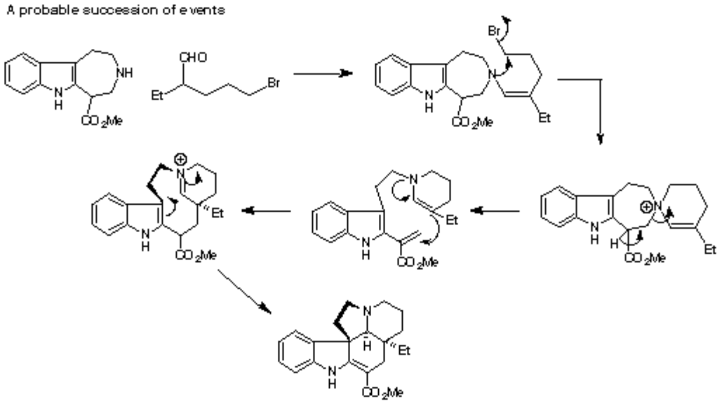
Provide a detailed mechanism for the illustrated transformation.



From the product, take one chemical step back

By inspection of starting material, the N and C atoms should be connected

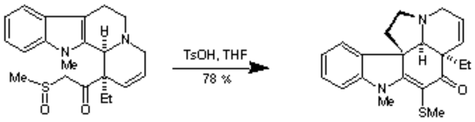
A probable succession of events



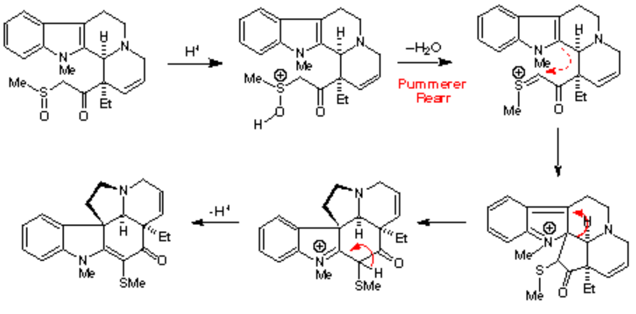
## Problem 146

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1985**, *50*, 961

An interesting rearrangement which also results in the construction of this same ring system (Question 4) has been reported by Langlois & coworkers (*J. Org. Chem.* 1985, *50*, 961). This rearrangement is illustrated below.



Provide a detailed mechanism for the illustrated transformation. Use three-dimensional representations, where relevant, to illustrate the stereochemical aspects of the individual steps.

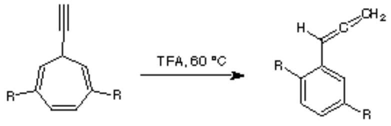


## Problem 147

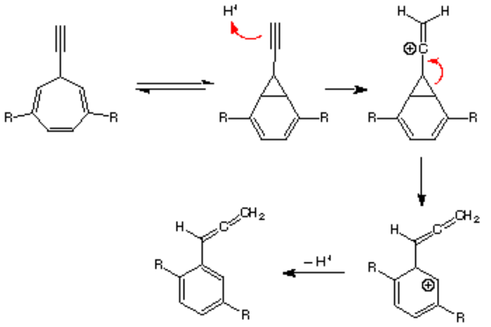
Contributer: **David A. Evans**
Citation: *Organic Lett.* **2000**, *2*, 3011

Kitagawa and coworkers (Org. Lett. 2000, 2, 3011) have recently described the trifluoroacetic acid (TFA) catalyzed rearrangement illustrated below.

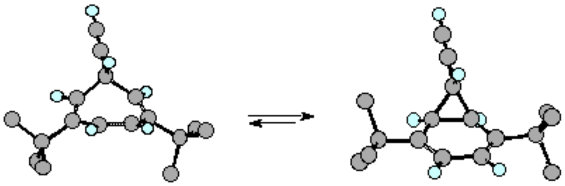
| substituent | rel rate |
|---|---|
| R = H | 1 |
| R = t-Bu | 370 |



Part A. Provide a concise mechanism for this reaction in the space below.



Part B. Please rationalize the rate difference for the two substrates. *Hint: In addressing this final point I recommend that you build a model of the starting cycloheptatriene.*

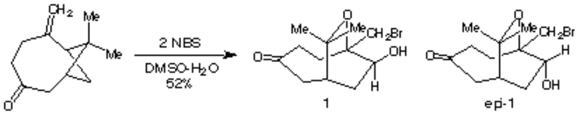


The equilibrium between the cycloheptatriene (CHT) to the norcaradiene (NCD) isomer may be perturbed by substituents at the indicated positions. In the case under discussion, it has been observed by the authors that tert-butyl substitution increases the concentration of the tert-Butyl-NCD isomer thus increasing the rate of the subsequent acid-catalyzed transformation to product.

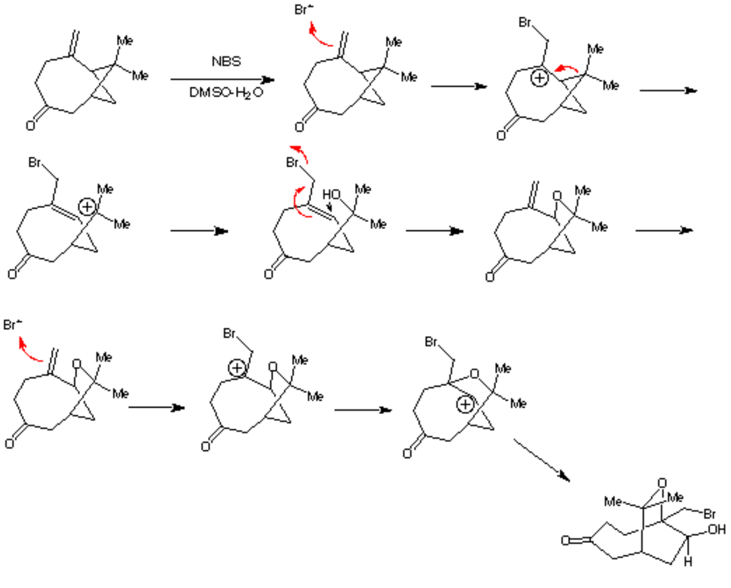
## Problem 148

Contributer: **David A. Evans**
Citation: *SynLett* **1997**, 1161

Mehta and coworkers (*SynLett* 1997, 1161) have recently described the *N*-bromosuccinimide (NBS) promoted rearrangement illustrated below. While the product was assigned the exo stereochemistry as illustrated in 1, DAE feels that the epi-1 structure cannot be ruled out.



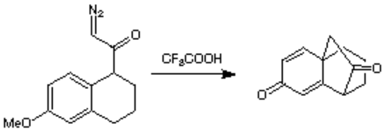
Provide a concise mechanism for this reaction in the space below.



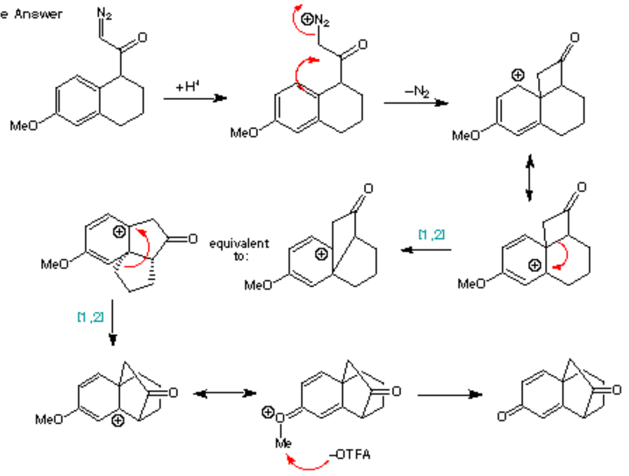
## Problem 150

Contributer: **David A. Evans**
Citation:

Provide a concise mechanism for the indicated reaction in the space below.



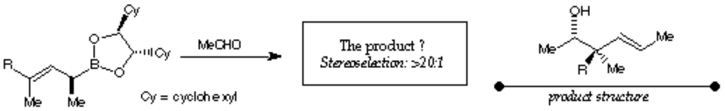
The Answer



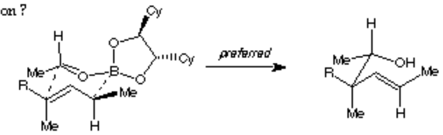
## Problem 152

Contributer: **David A. Evans**
Citation: **1991**, 1203

The following stereoselective transformation has been reported by Hoffmann (*Liebig's Ann. Chem.* 1991, 1203). Provide the stereostructure of the major product and rationalize the stereochemical outcome of the process.



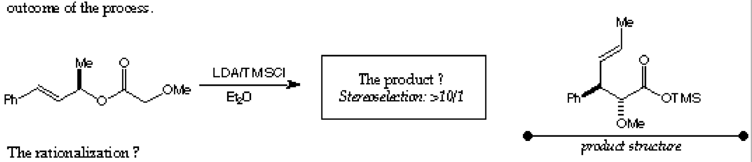
The rationalization ?



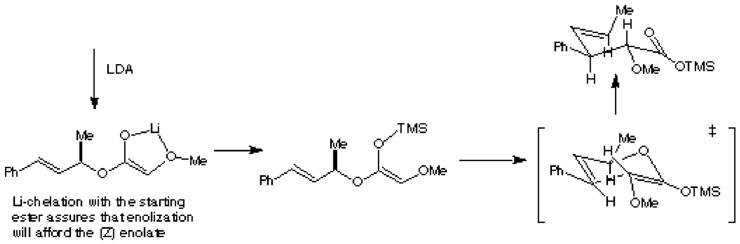
## Problem 153

Contributer: **David A. Evans**
Citation:

Provide the stereostructure of the major product of the indicated transformation, and rationalize the stereochemical outcome of the process.



The rationalization ?



Li-chelation with the starting ester assures that enolization will afford the (Z) enolate

## Problem 169

Contributer: **David A. Evans**
Citation:

Consult the cited reference for an answer to this question

## Problem 170

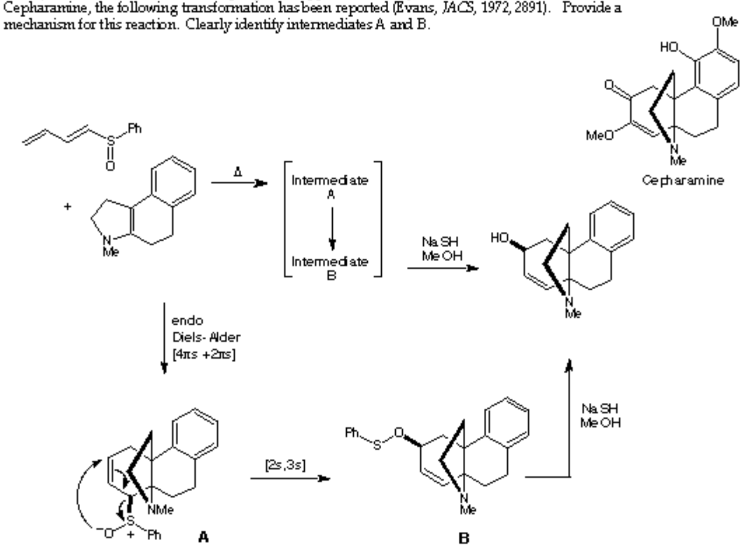
Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2000**, *65*, 8564

Consult the cited reference for an answer to this question

## Problem 175

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1972**, 2891

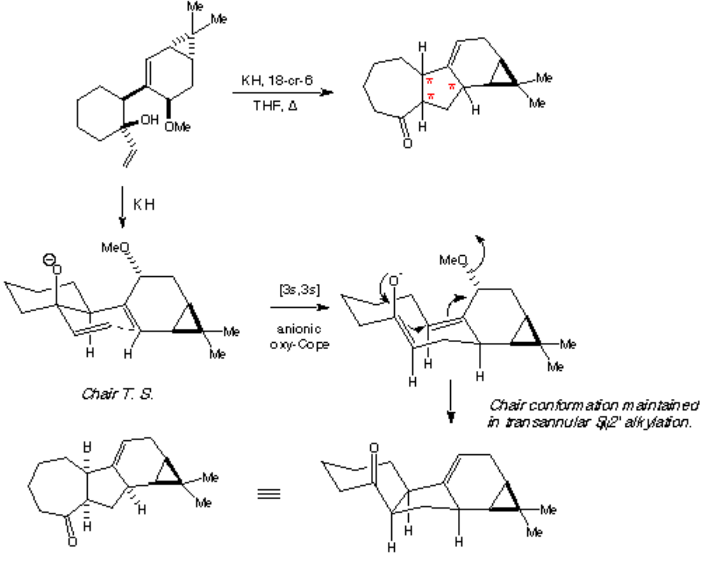
In conjunction with efforts to develop a general approach to the synthesis of the hasubanan alkaloid Cepharamine, the following transformation has been reported (Evans, *JACS*, 1972, 2891). Provide a mechanism for this reaction. Clearly identify intermediates A and B.



## Problem 176

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1989**, 5205

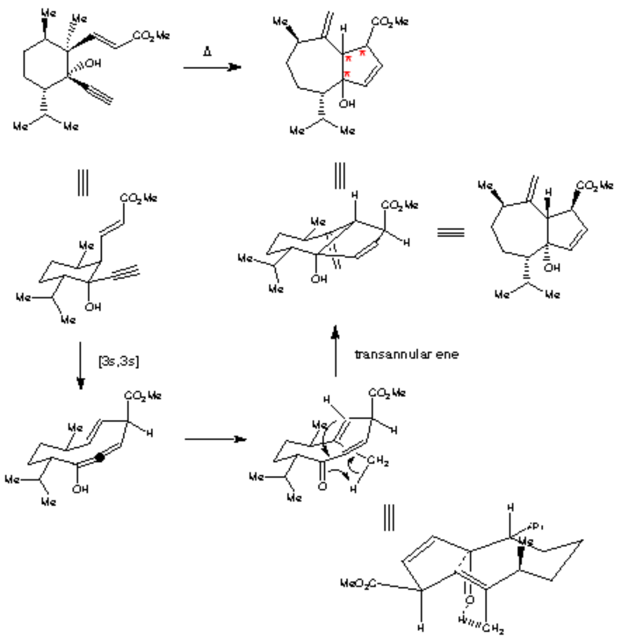
Provide a mechanism for the following transformation that predicts the stereochemistry at the starred (*) carbon atoms (Paquette, *JOC*, 1989, 5205).



## Problem 177

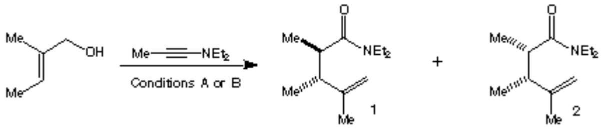
Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1998**, *39*, 4133

Provide a mechanism that predicts the observed stereochemistry at the starred (*) carbon atoms (Rajagopalan, *Tetrahedron Lett.* 1998, *39*, 4133). Draw the starting material, each intermediate, and the product clearly in 3D.



**Problem 178** Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1979**, 882

Provide a mechanistic rationale for the following observations (Bartlett, P. A. *JOC*, 1979, 882).
Note: the products were shown to be stable to the reaction conditions.

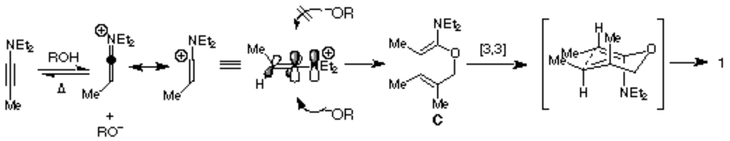


Conditions A: Steady addition of ROH to ynamine.
Conditions B: ROH and ynamine stirred in the presence of a catalytic amount of $BF_3$•etherate in benzene for 4 days.

| Conditions | 1 : 2 |
|---|---|
| A | 10:1 |
| B | 1:10 |

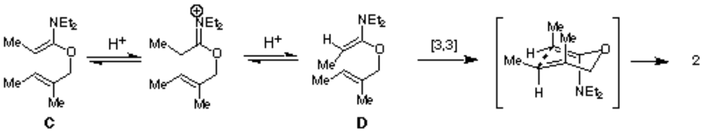
*The [3,3] sigmatropic rearrangement is a concerted, stereoselective process. Product stereochemistry is determined by the relative geometries at the termini of the reacting double bonds.*

Analysis of Conditions A



*Vinyl cations are linear, with the empty p-orbital orthogonal to the p-orbitals of the double bond. Alkoxide (or alcohol) will approach the keteniminium ion kinetically from the side of the double bond away from the Me group which leads to the (E) ketene N,O-acetal C.*

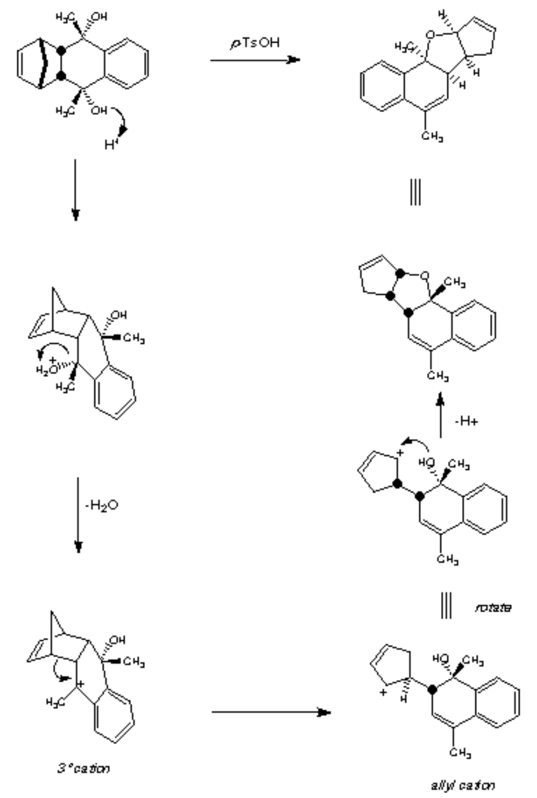
Analysis of Conditions B



*In the presence of additional acid and alcohol, the initially kinetically formed C can isomerize to the thermodynamically more stable (less $A^{1,3}$ strain) (Z) ketene N,O-acetal, D, before rearrangement occurs.*

**Problem 183** Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1990**, 5357

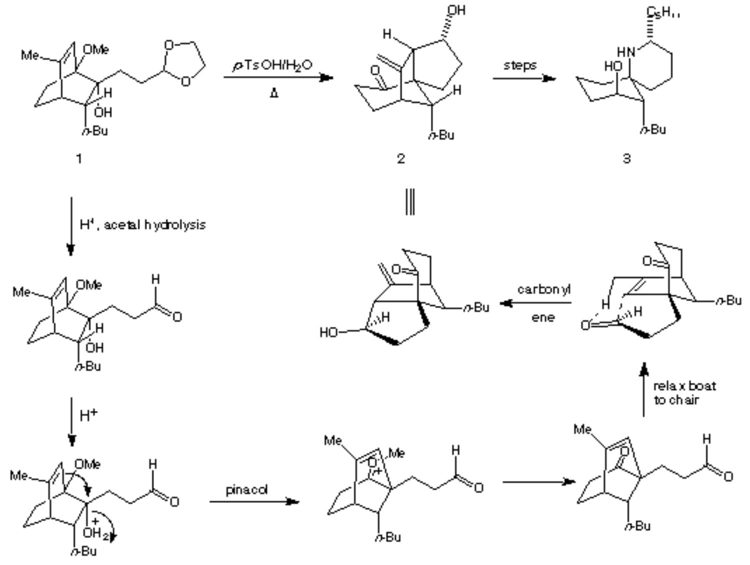
Provide a mechanism for the following transformation (Coxon, *Tetrahedron Lett.* 1990, 5357).



## Problem 184

Contributer: **David A. Evans**
Citation: *Chem. Commun.* **1997**, 2263

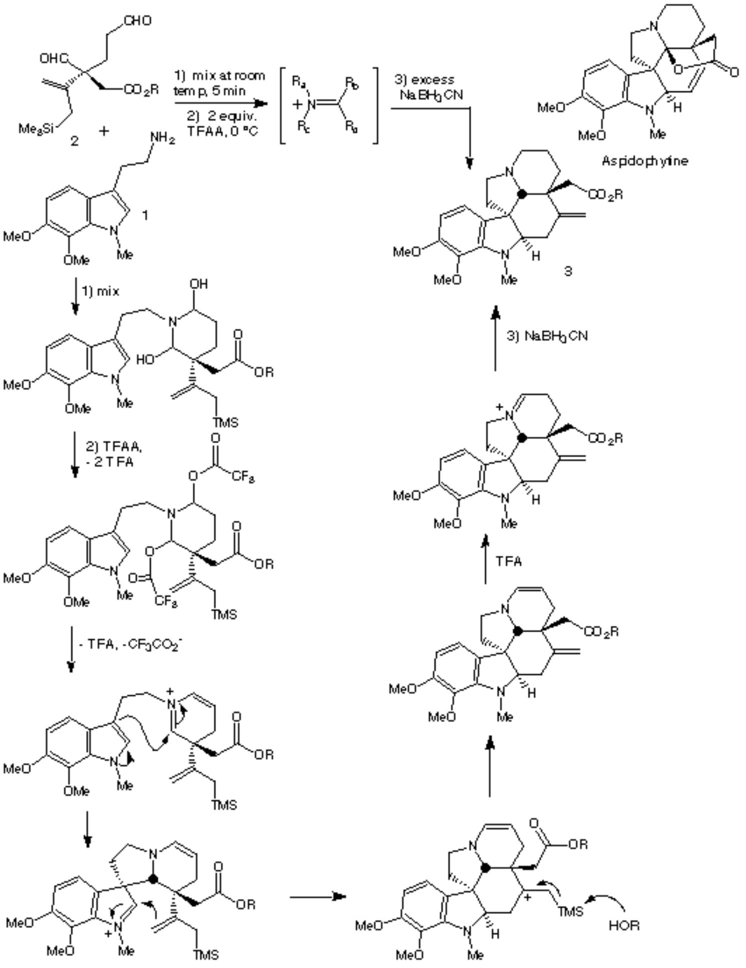
The key step in Kim's synthesis of perhydrohistrionicotoxin, 3, was the conversion of intermediate 1 to ketone 2 in a single acid-catalyzed transformation (*Chem. Commun.*, 1997, 2263). Provide a mechanism for the conversion of 1 to 2 that accounts for the observed stereochemistry.



## Problem 185

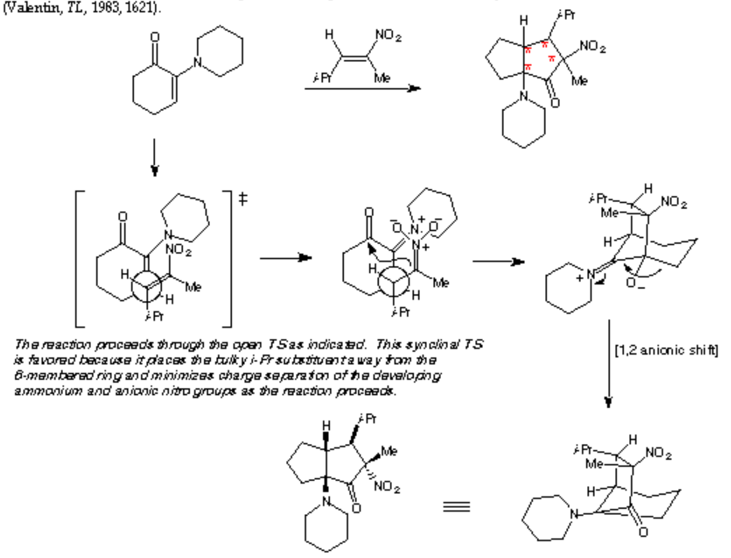
Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1999**, *121*, 6771

During Corey's recent synthesis of Aspidophytine (*JACS* 1999, *121*, 6771), the pivotal intermediate 3 was assembled by the union of 1 and 2 under the specified conditions. Provide a mechanism for this single-pot transformation.



**Problem 188** Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1983**, 1621

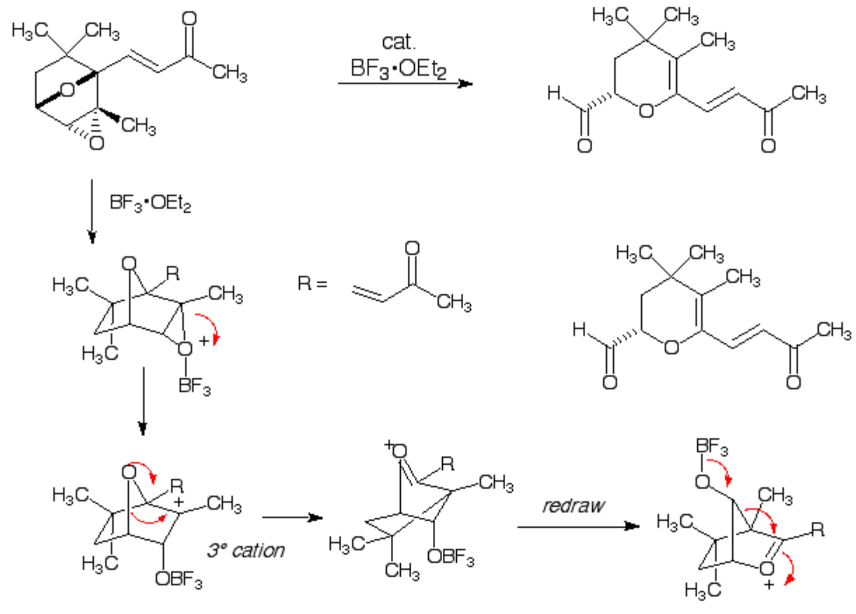
Provide a mechanism for the following reaction that predicts the stereochemistry at the starred (*) carbon atoms (Valentin, *TL*, 1983, 1621).



*The reaction proceeds through the open TS as indicated. This synclinal TS is favored because it places the bulky i-Pr substituent away from the 6-membered ring and minimizes charge separation of the developing ammonium and anionic nitro groups as the reaction proceeds.*

**Problem 192** Contributer: **David A. Evans**
Citation: *Chem. Commun.* **1992**, 342

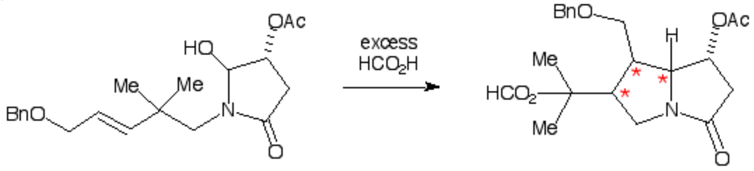
Provide a mechanism for the following reaction (*Chem. Comm*, **1992**, 342).



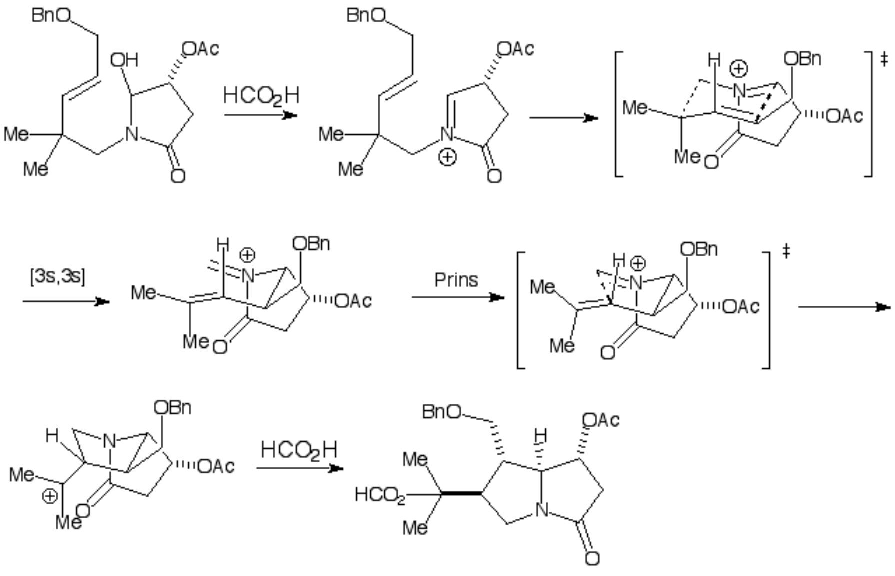
## Problem 193

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1985**, 235

Provide a mechanism for the indicated transformation that predicts the observed stereochemistry at the three starred (*) carbon atoms (*JOC*, **1985**, 235).



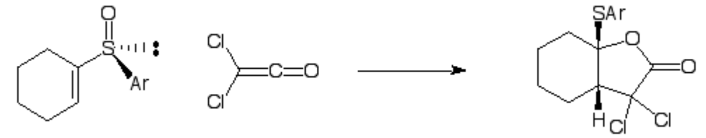
**Answer**



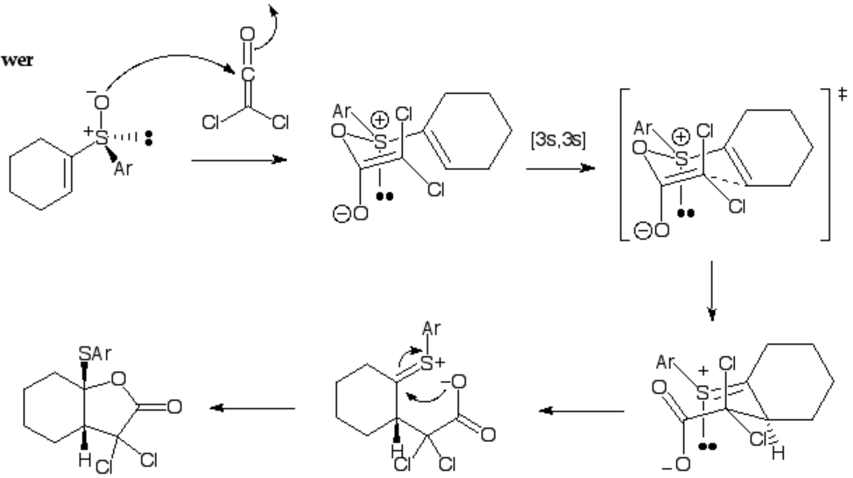
## Problem 195

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1984**, 7643

Provide a mechanism for the indicated transformation that accounts for the observed stereochemical outcome (*JACS*, **1984**, 7643).



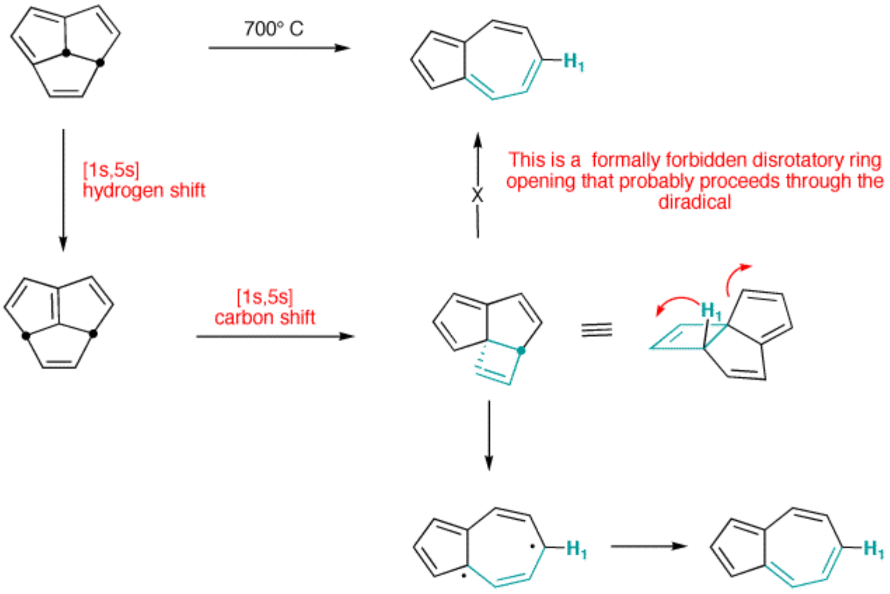
**Answer**



## Problem 198

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1973**, 2724

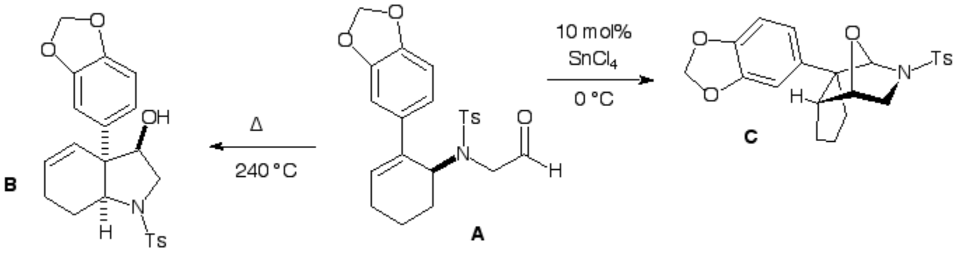
Provide a mechanism for the thermal conversion of triquinacene to azulene (*JACS*, **1973**, 2724).


700° C
H1
[1s,5s]
hydrogen shift
X
This is a formally forbidden disrotatory ring opening that probably proceeds through the diradical
[1s,5s]
carbon shift
≡
H1
H1
H1

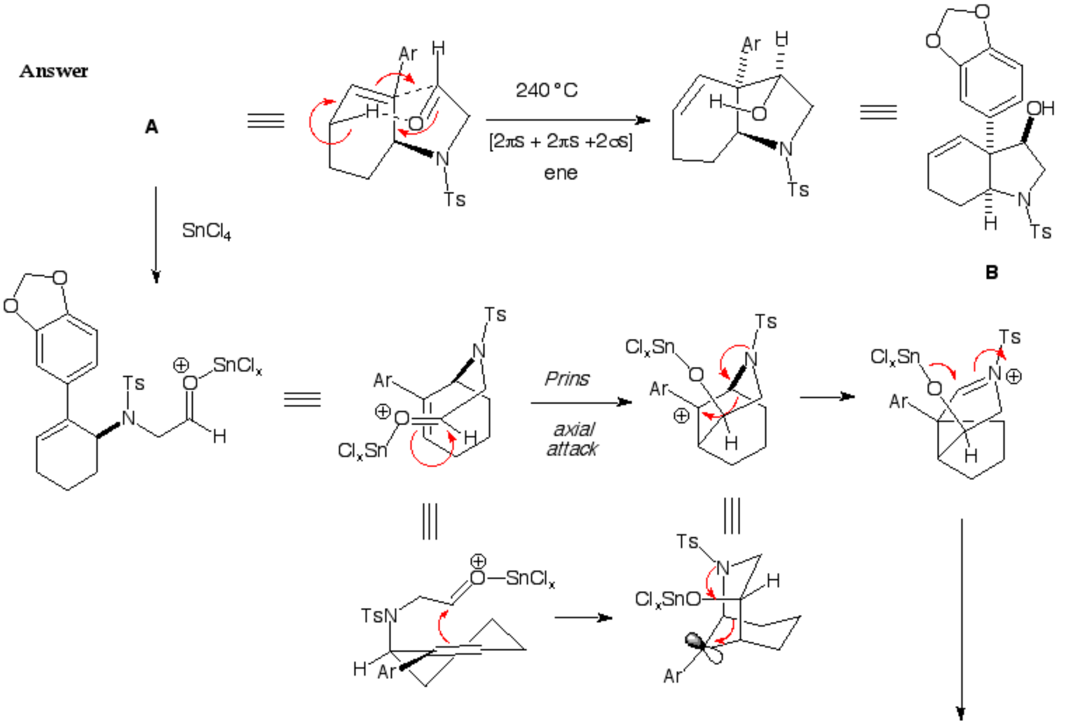
## Problem 203

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1998**

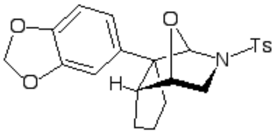
Provide mechanisms that account for the stereoselective formation of the products obtained by treatment of aldehyde **A** to the conditions shown below. Briefly comment on the difference in reactivity under the two sets of conditions (*JOC*, **1998**, 7586).



**Answer**



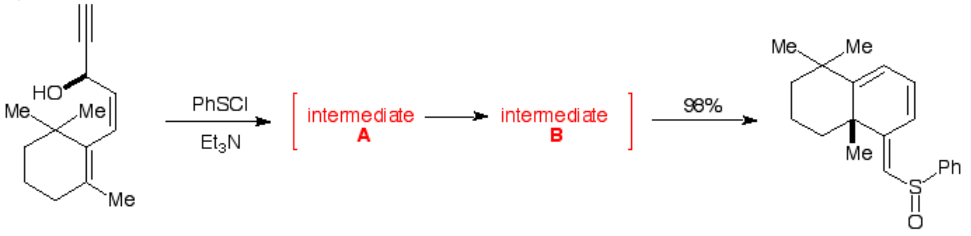
*Thermal conditions promote a concerted ene reaction. Under Lewis acidic conditions, a stepwise mechanism predominates where a Prins reaction leads to the stablized benzylic cation. Nitrogen assisted ring contraction leads to the iminium ion which is quenched by the alkoxide.*



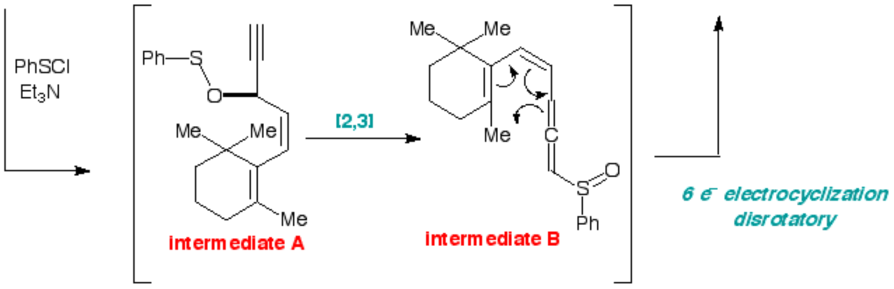
C

**Problem 212** Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1985**, *107*, 1034

Provide a mechanism for the following transformation. Identify **A** and **B** in your reaction sequence. (Okamura JACS **1985**, *107*, 1034).



**Answer**

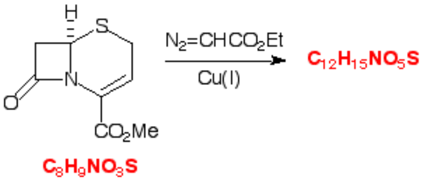


## Problem 213

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1972**, 2923

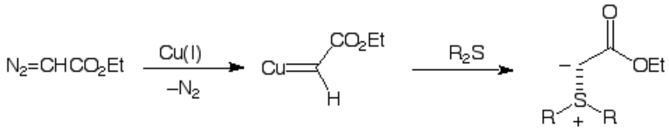
Based on the knowledge that you have acquired in this course, predict the product of the reaction and provide a mechanism for the transformation. In addition to the molecular formula of the product, the NMR spectrum indicated the presence of three olefinic H's, one OMe fragment, and one OEt fragment (*Tet. Lett.* **1972**, 2923).

To receive full credit, you must also illustrate how any new stereochemical relationships are created.

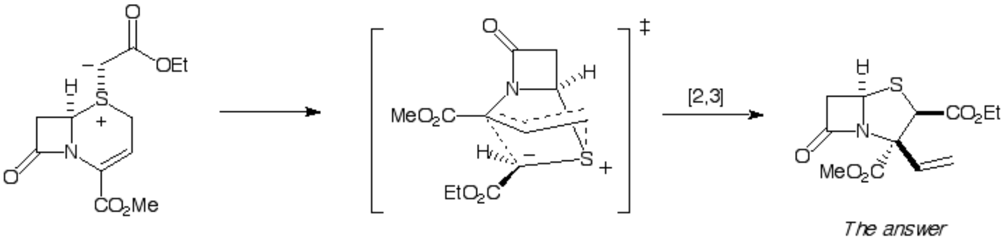


**Answer** *The key to solving this problem is the recognition of a [2,3] sigmatropic rearrangement.*

**Sulfur ylid formation:**



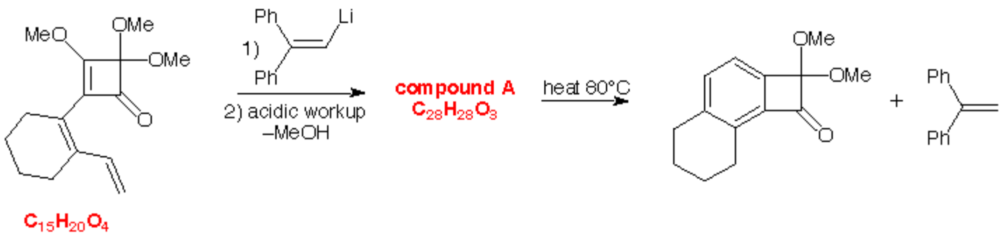
**The rearrangement:**



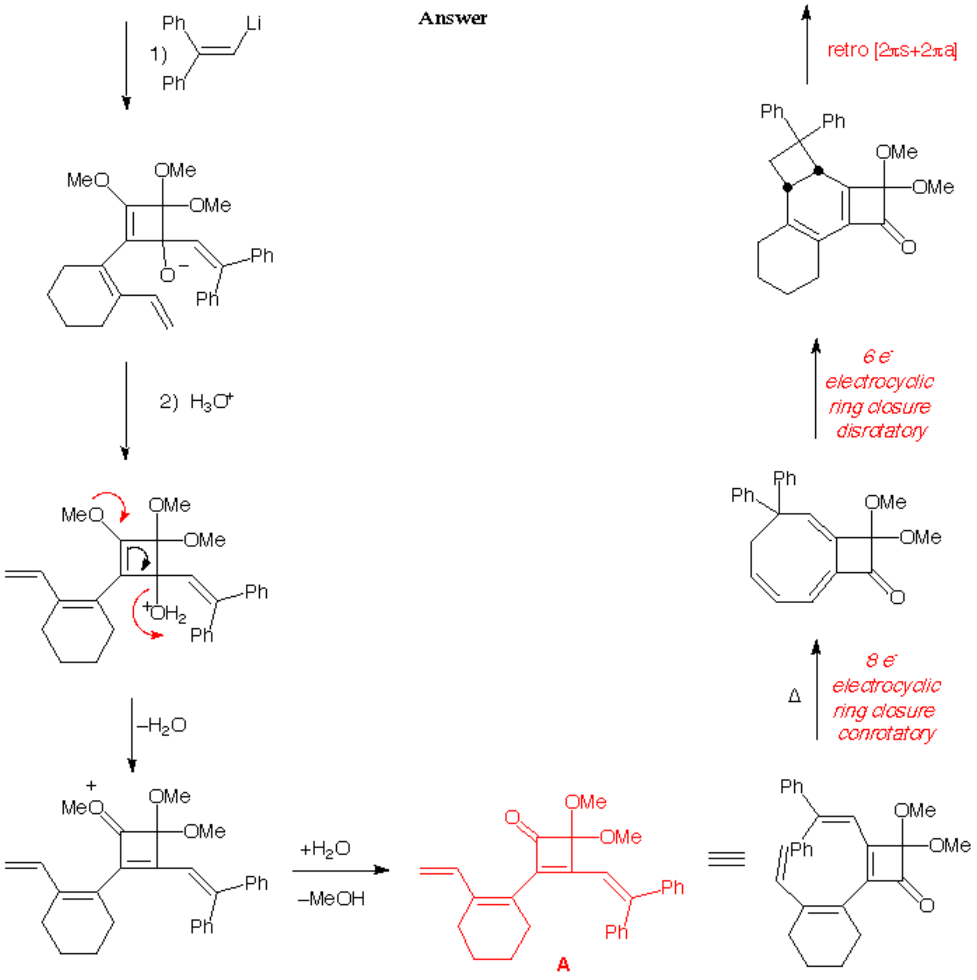
## Problem 215

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1999**, *64*, 2170

Provide a mechanism for the following set of transformations (*J. Org. Chem.* **1999**, *64*, 2170). It should be noted that compound **A** exhibits a strong carbonyl frequency in the infrared spectrum. Clearly indicate the structure of compound **A** and the relative stereochemistry of any chiral intermediates.



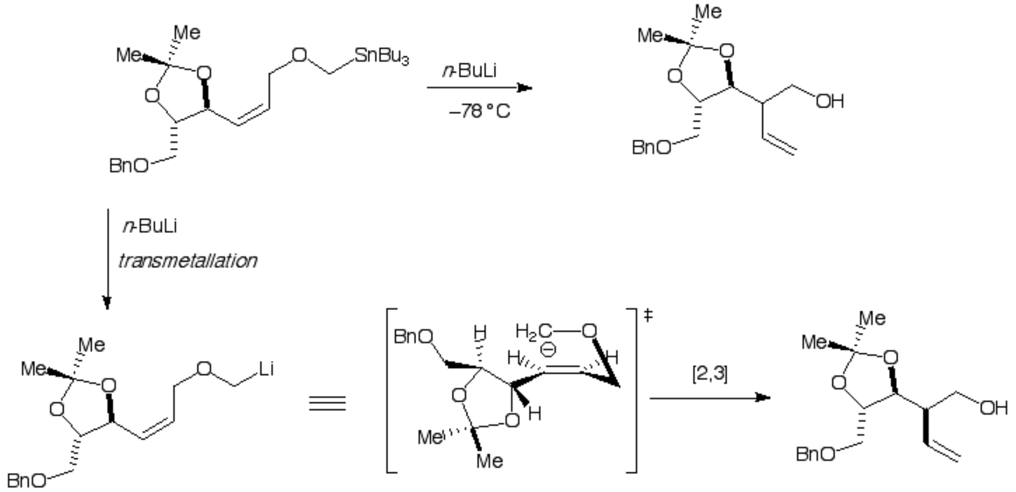
**Answer**



**Problem 216** Contributer: **David A. Evans**

Citation: *Tetrahedron* **1999**, *55*, 13369

Provide a mechanism for this rearrangement that predicts the major product diastereomer (*Tetrahedron*, **1999**, *55*, 13369).

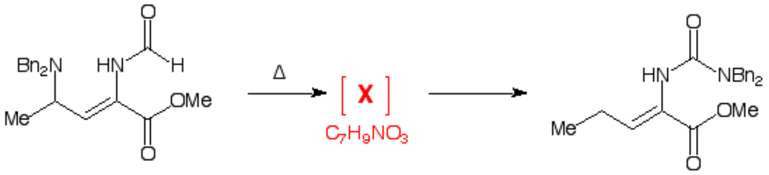


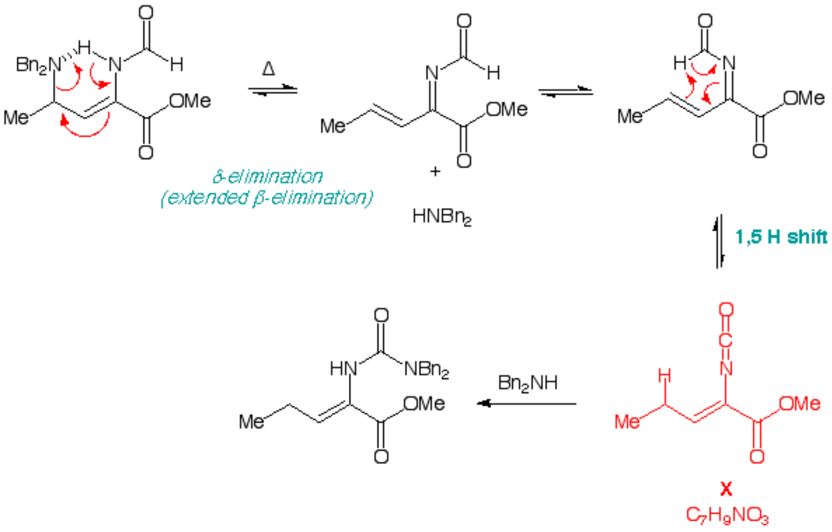
*Apply the "Houk model": the allylic C-O bond (best acceptor) is placed orthogonal to the C=C bond and antiperiplanar to the attacking carbanion.*

## Problem 217

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1993**, 579

Provide a mechanism for the following reaction. The reaction was shown to proceed through isocyanate (RNCO) **X**. Identify **X** (Kende, *TL*, **1993**, 579).

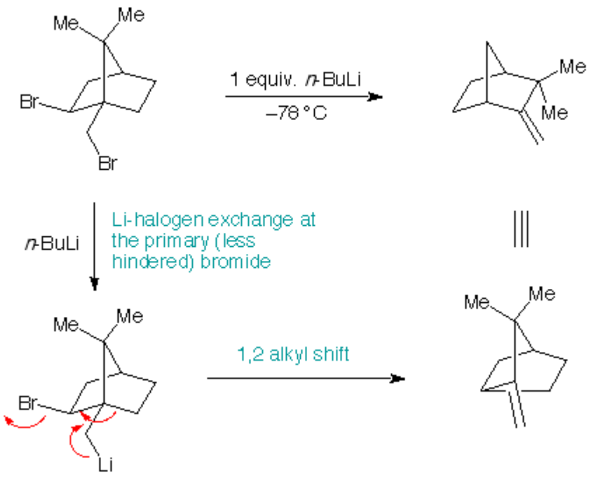




## Problem 218

Contributer: **David A. Evans**
Citation: *Angew. Chem.* **1998**, 3173

Provide a plausible mechanism for the following anionic rearrangement (Schlosser, *ACIE*, **1998**, 3173).



*A stepwise mechanism (fragmentation followed by $S_N2$) can not be ruled out, however excellent orbital overlap (σ C-C → σ* C-Br) suggests the 1,2 shift is highly likely.*

**Problem 225** Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1983**, *48*, 2685

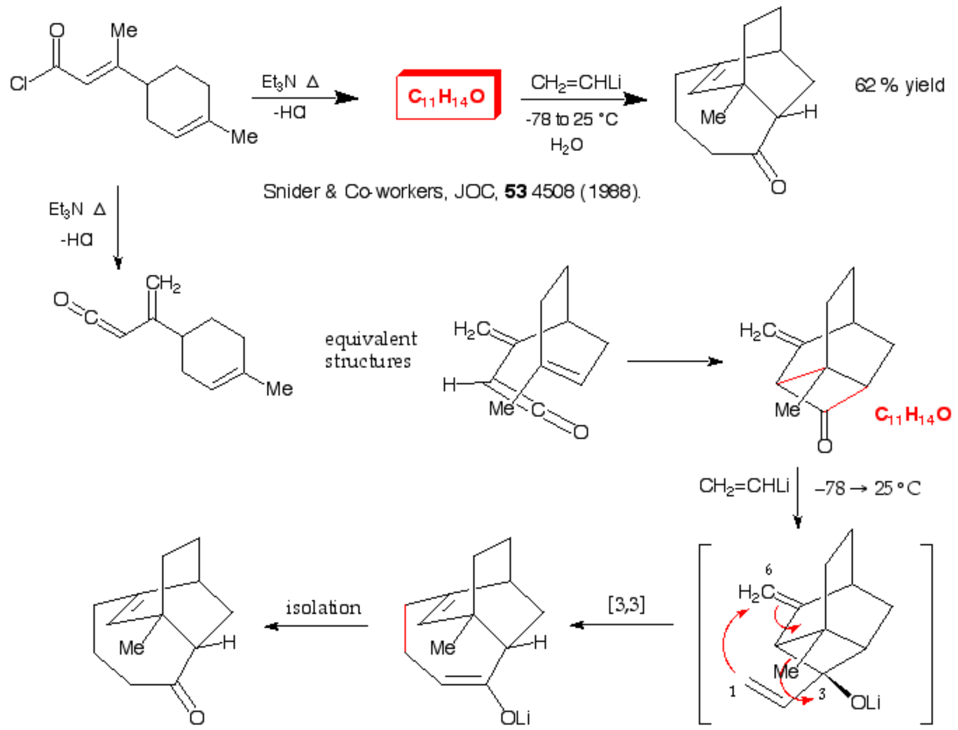
Consult the cited reference for an answer to this question

**Problem 230** Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1986**, *110*, 6556

Consult the cited reference for an answer to this question

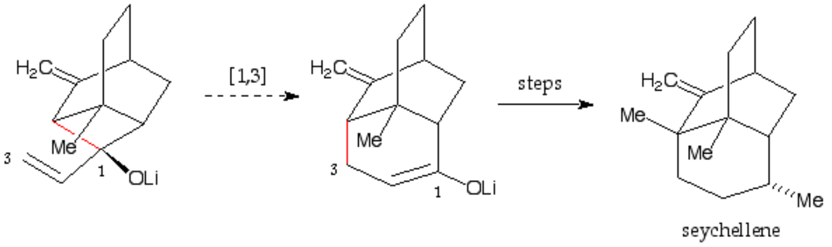
**Problem 231** Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1988**, *53*, 4508

Write a plausible mechanism for the two-step illustrated below. Where stereochemistry is an issue, draw the conformation of the reacting entity which illustrates the relationship between chiral and prochiral centers.



Snider & Co-workers, JOC, **53** 4508 (1988).

**Snider's Original Plan:**

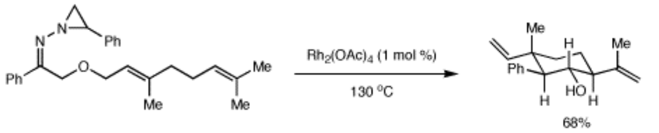


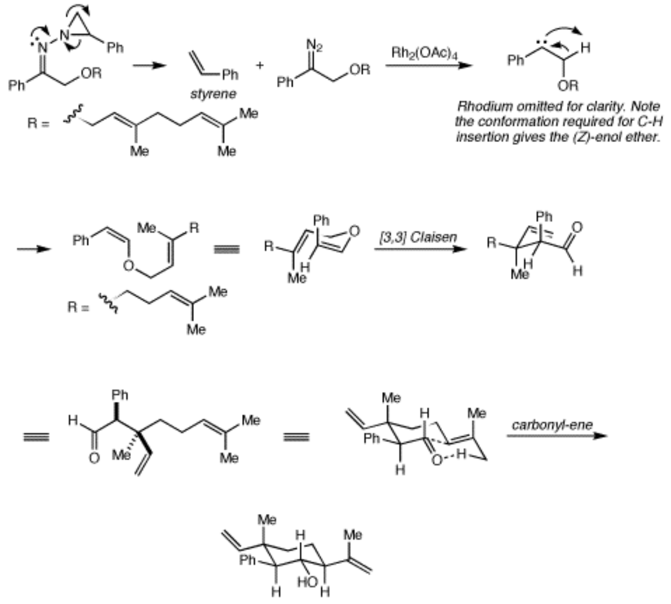
**Problem 233** Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2001**, *123*, 5152

Consult the cited reference for an answer to this question

**Problem 234** Contributer: **Carl A. Morales**
Citation: *J. Am. Chem. Soc.* **2002**, *124*, 12426

Recent work from the Stoltz labs on non-carbonyl-stabilized metallocarbenoids has fostered "the development of a tandem rhodium-catalyzed Bamford-Stevens/thermal aliphatic Claisen rearrangment sequence." Please demonstrate your appreciation for this methodology by providing a plausible mechanism for the impressive transformation below, noting the relative stereochemistry of the product and the fact that styrene is a byproduct of the reaction.





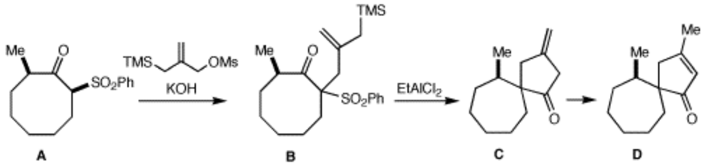
Rhodium omitted for clarity. Note the conformation required for C-H insertion gives the (Z)-enol ether.

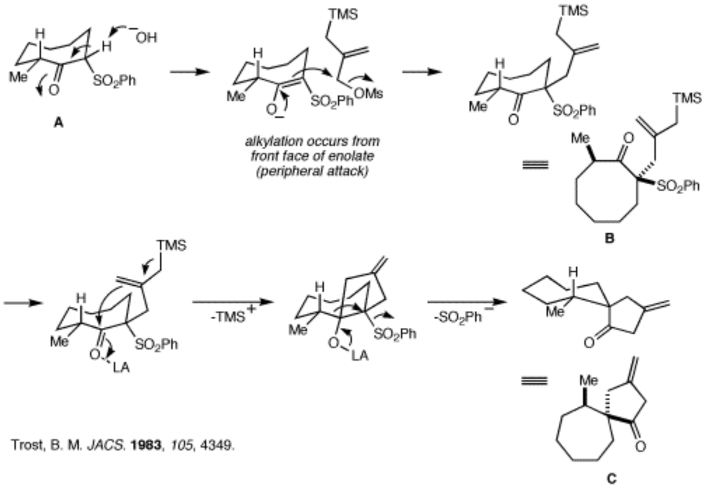
Stoltz, B. M. *JACS.* **2002**, *124*, 12426.

## Problem 237

Contributer: **Carl A. Morales**
Citation: *J. Am. Chem. Soc.* **1983**, *105*, 4349

The following two step reaction sequence converts starting material **A** into **C** where under the conditions of the second step, **C** is isomerized to product **D**. Provide mechanisms for the conversion of **A** to **B** and for **B** to **C** and predict the stereochemistry of **B** and **C** using clear 3D representations to justify your choice.





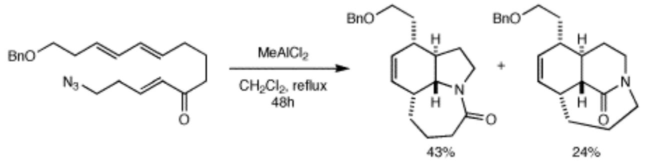
alkylation occurs from front face of enolate (peripheral attack)

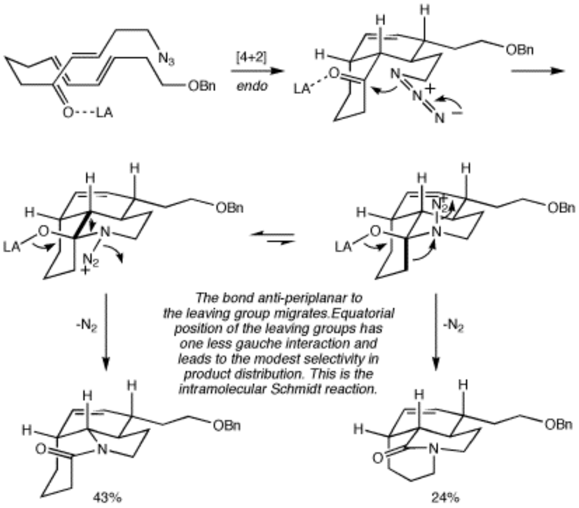
Trost, B. M. *JACS.* **1983**, *105*, 4349.

## Problem 240

Contributer: **Carl A. Morales**
Citation: *Angew. Chem.* **2002**, *41*, 4492

In a recent report of a formal synthesis of stenine, researchers reported a tandem polycyclization which afforded the following major and minor products. Please propose a mechanism for this transformation which accounts for both products, their relative stereochemistry, and their relative distribution.





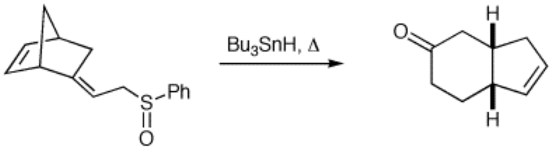
*The bond anti-periplanar to the leaving group migrates.Equatorial position of the leaving groups has one less gauche interaction and leads to the modest selectivity in product distribution. This is the intramolecular Schmidt reaction.*

Aube, J. *Ang. Chem. Int. Ed*, **2002**, *41*, 4492.

## Problem 241

Contributer: **David A. Evans**
Citation: *Angew. Chem.* **2002**, *41*, 4323

Renaud has disclosed an interesting reaction cascade (*Angew. Chem. Int. Ed.* **2002**, *41*, 4323). One of the reported transformations is illustrated below. The paper includes six related examples.

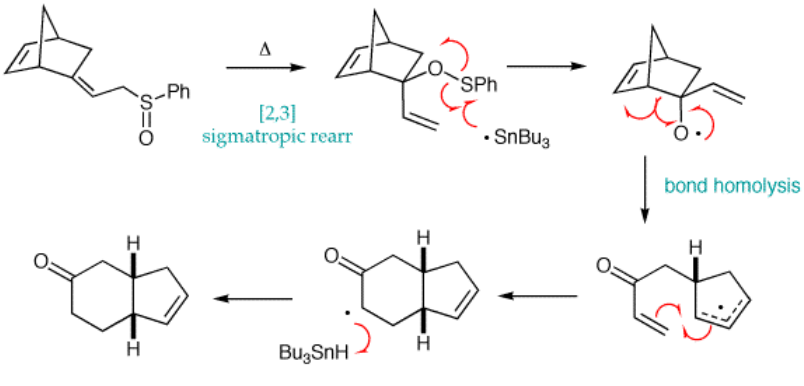


46% yield

Provide a plausible mechanism for this reaction cascade. Your answer should include three-dimensional structures that accurately depict ground and transition state representations.

**For related reactions, see Problems 83, 175, 212 For related literature, see also,** "Allylic Sulfoxides: Useful Intermediates in Organic Synthesis". Evans, D. A.; Andrews, G. C. *Accts. Chem. Res.* **1974**, *7*, 147-155.

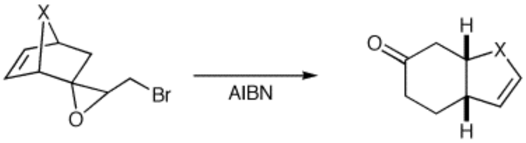
Answer



## Problem 242

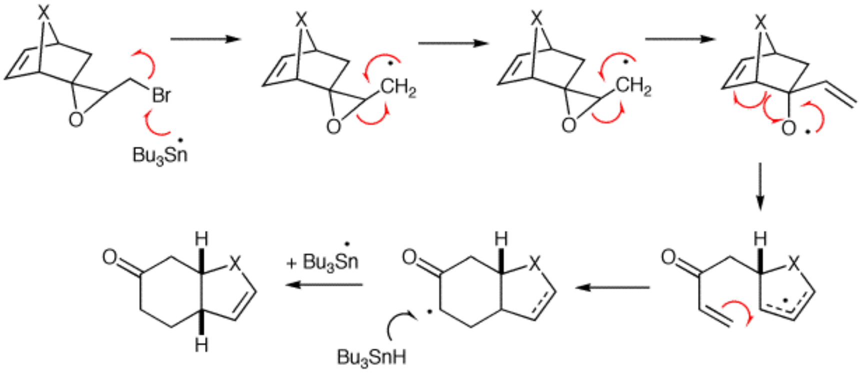
Contributer: **David A. Evans**
Citation: *Angew. Chem.* **2002**, *41*, 4321-4323

Renaud has disclosed an interesting reaction cascade (*Angew. Chem. Int. Ed.* **2002**, *41*, 4321). One of the reported transformations is illustrated below. The paper includes related examples.



46-60% yield

Provide a plausible mechanism for this reaction cascade. Your answer should include three-dimensional structures that accurately depict ground and transition state representations.



## Problem 243

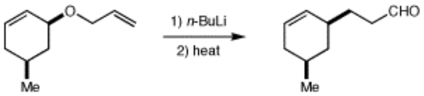
Contributer: **David A. Evans**
Citation: *Chem. Commun.* **2003**, 798

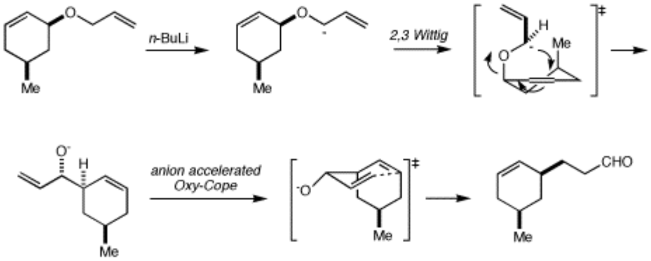
Consult the cited reference for an answer to this question

## Problem 258

Contributer:
Citation: *Tetrahedron Lett.* **1982**, *23*, 3931

Provide a mechanism for the following transformation. Include the stereochemistry of all intermediates and provide 3D drawings of all transition states.



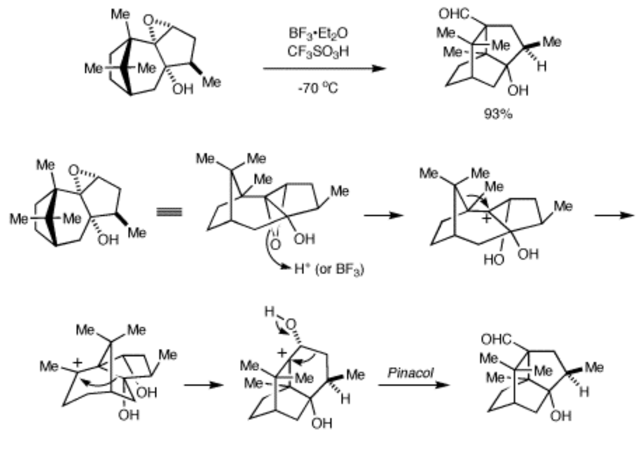


T. Nakai *Tetrahedron Lett.* **1982**, *23*, 795

## Problem 260

Contributer: **Carl A. Morales**
Citation: *Strategies & Tactics in Org. Syn.* **1991**, *3* , 165-198

Using 3D representations, provide a mechanism for the transformation below.

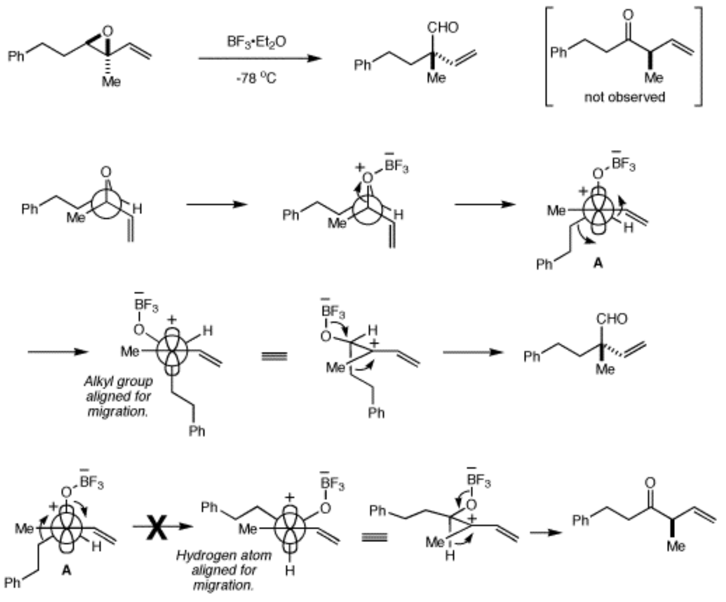


*Strategies and Tactics in Organic Synthesis*, vol. 3; 1991, p 165-198.

## Problem 261

Contributer: **Carl A. Morales**
Citation: *J. Am. Chem. Soc.* **1995**, *117*, 7379

Please provide a mechanism for the following transformation that clearly explains the exclusive formation of the indicated aldehyde product and the lack of ketone.


BF$_3$•Et$_2$O
-78 °C
not observed
A
Alkyl group aligned for migration.
Hydrogen atom aligned for migration.

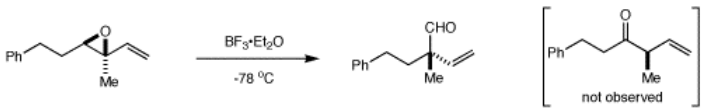
*According to the principle of least motion, for the 1,2-shift to occur carbocation* ***A*** *must rotate to place either the alkyl group or the hydrogen atom in a position to overlap with the vacant p orbital. Rotation in a counterclockwise sense to align the alkyl group for migration requires the hydrogen atom to eclipse the vinyl moiety. This torsional interaction is less costly than the eclipsing of the alkyl group and methyl group caused by clockwise rotation.*

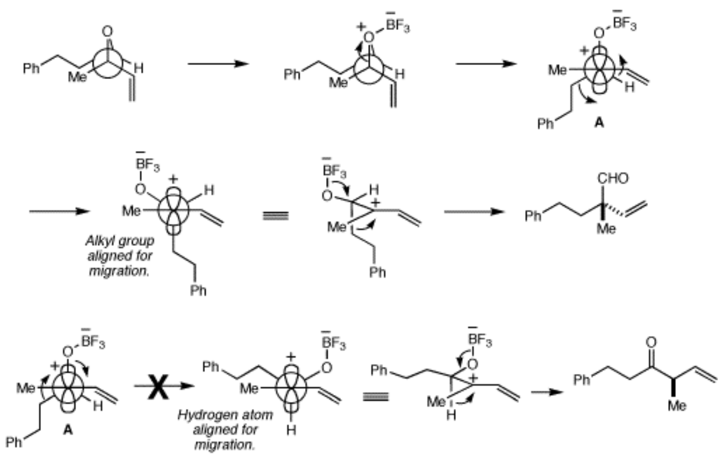
Jung, M. *JACS*, **1995**, 7379.

## Problem 262

Contributer: **Carl A. Morales**
Citation: *J. Am. Chem. Soc.* **1995**, *117*, 7379

Please provide a mechanism for the following transformation that clearly explains the exclusive formation of the indicated aldehyde product and the lack of ketone.




Ph
Me
O
H
BF3
A
Alkyl group aligned for migration.
CHO
Hydrogen atom aligned for migration.
X

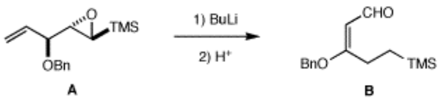
*According to the principle of least motion, for the 1,2-shift to occur carbocation **A** must rotate to place either the alkyl group or the hydrogen atom in a position to overlap with the vacant p orbital. Rotation in a counterclockwise sense to align the alkyl group for migration requires the hydrogen atom to eclipse the vinyl moiety. This torsional interaction is less costly than the eclipsing of the alkyl group and methyl group caused by clockwise rotation.*

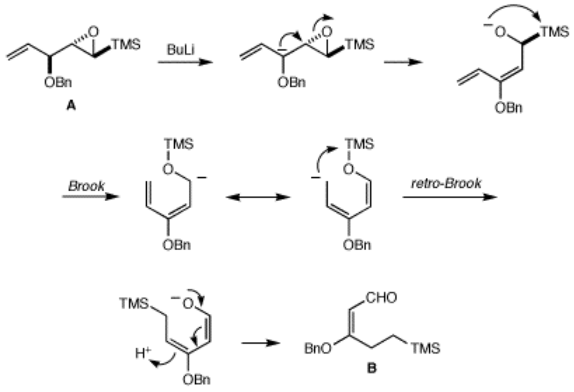
Jung, M. *JACS*, **1995**, 7379.

## Problem 264

Contributer: **Carl A. Morales**
Citation: *J. Org. Chem.* **1996**, *61*, 9065

In a recent study, the authors began life with chiral epoxide A and obtained aldehyde B following the conditions below. Provide a mechanism that accounts for this stereo-destructive process. You do not have to explain the double bond geometry in the product.



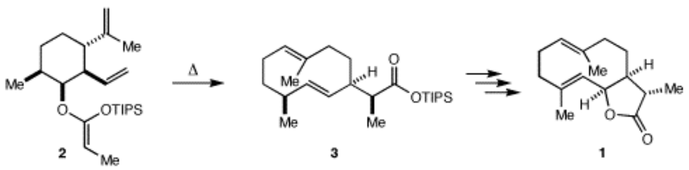


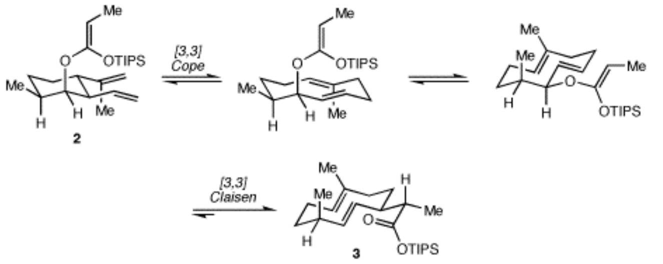
Jung, M. *JOC*, **1996**, *61*, 9065.

## Problem 265

Contributer: **Carl A. Morales**
Citation: *J. Org. Chem.* **1986**, *51*, 5503

The following reaction was a key step in the enantioselective synthesis of (+)-dihydrocostunolide 1. Provide a reasonable mechanism for the conversion of 2 to 3 using clear 3D representations.



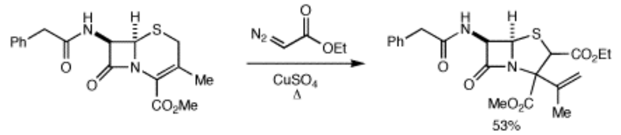


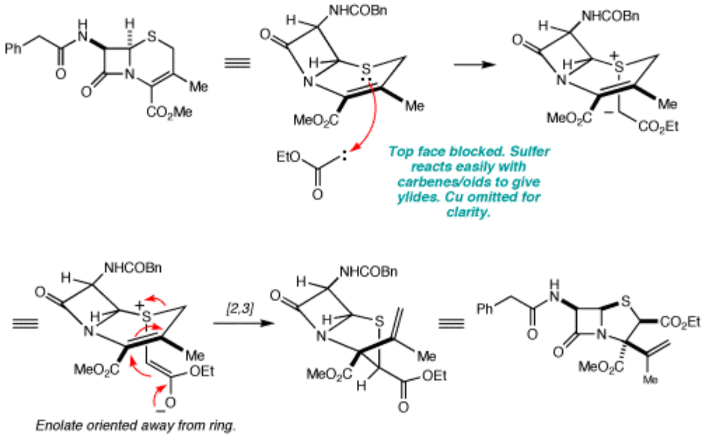
Raucher, *J. Org. Chem.* **1986**, *51*, 5503.

## Problem 266

Contributer: **Carl A. Morales**
Citation: *Tetrahedron Lett.* **1972**, 2923

Provide a mechanism for the following transformation and predict the stereochemistry of the product (Yashimoto, M. *Tetrahedron Lett.* **1972**, 2923).





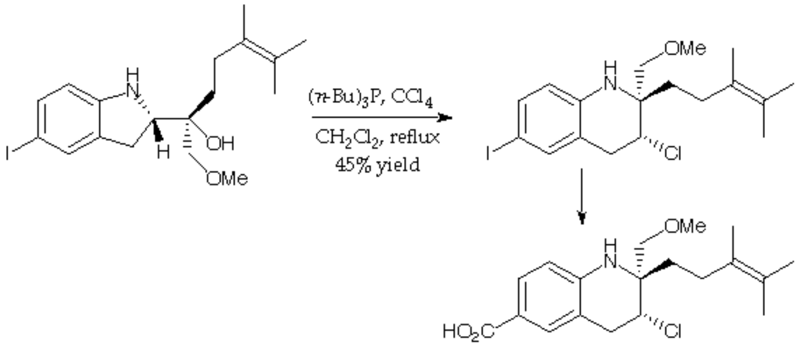
*Top face blocked. Sulfer reacts easily with carbenes/oids to give ylides. Cu omitted for clarity.*

*Enolate oriented away from ring.*

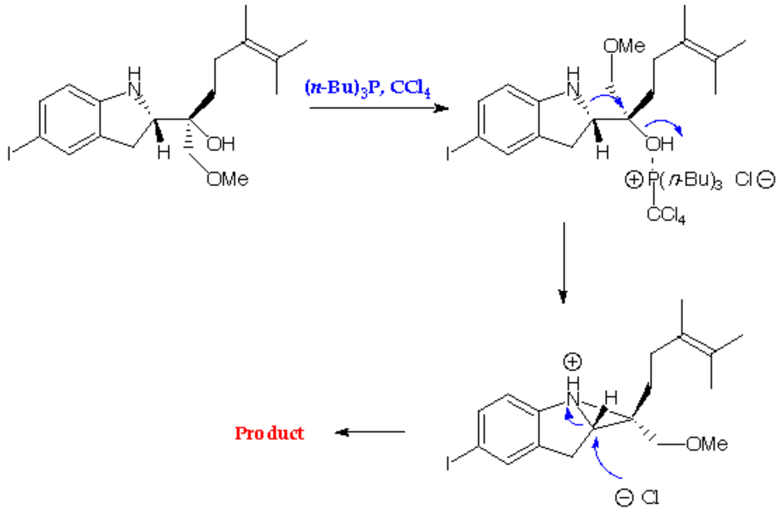
## Problem 279

Contributer: **Jake Janey**
Citation: *Angew. Chem.* **2003**, *42*, 2540-2543

Kogen has reported an interesting rearrangement of indoline-2-methanol to 2,2,3-trisubstituted tetrahydroquinoline (*Angew. Chem. Int. Ed., Engl.* **2003**, *42*, 2540-2543). Along with numerous examples, they reported a synthesis of (–)-virantmycin. Propose a plausible mechanism for this rearrangement.



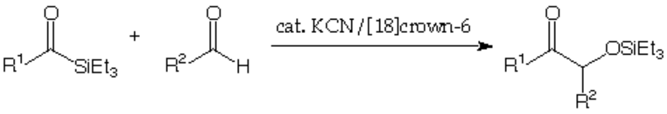
(–)-*virantmycin*



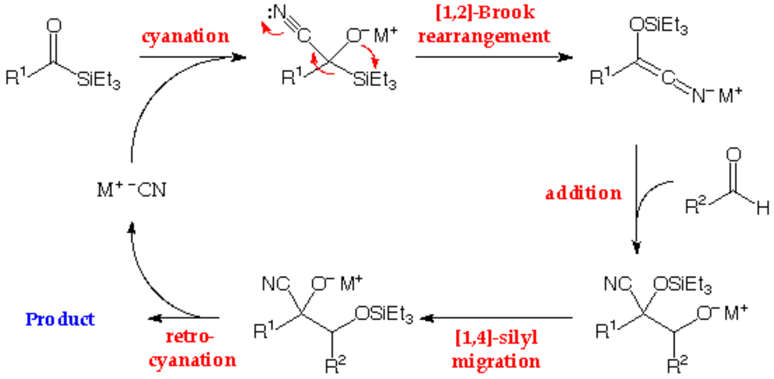
**Problem 280**

Contributer: **Jake Janey**
Citation: *Angew. Chem.* **2003**, *42*, 2534-2536

J. S. Johnson has reported a way of forming α-hydroxy ketones by a cross condensation of an aldehyde and an acylsilane catalyzed by KCN/[18]crown-6 (*Angew. Chem. Int. Ed., Engl.* **2003**, *42*, 2534). This reaction is quite general for forming a variety of α-hydroxy ketones. Provide a plausible mechanism for this cyanide catalyzed reaction.



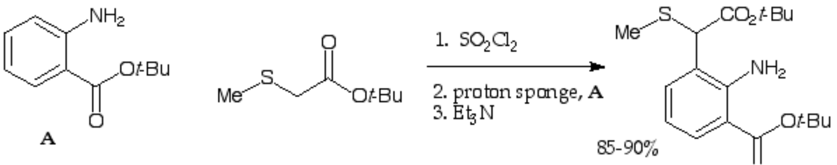
***Answer: Catalyzed cross silyl benzoin reaction***



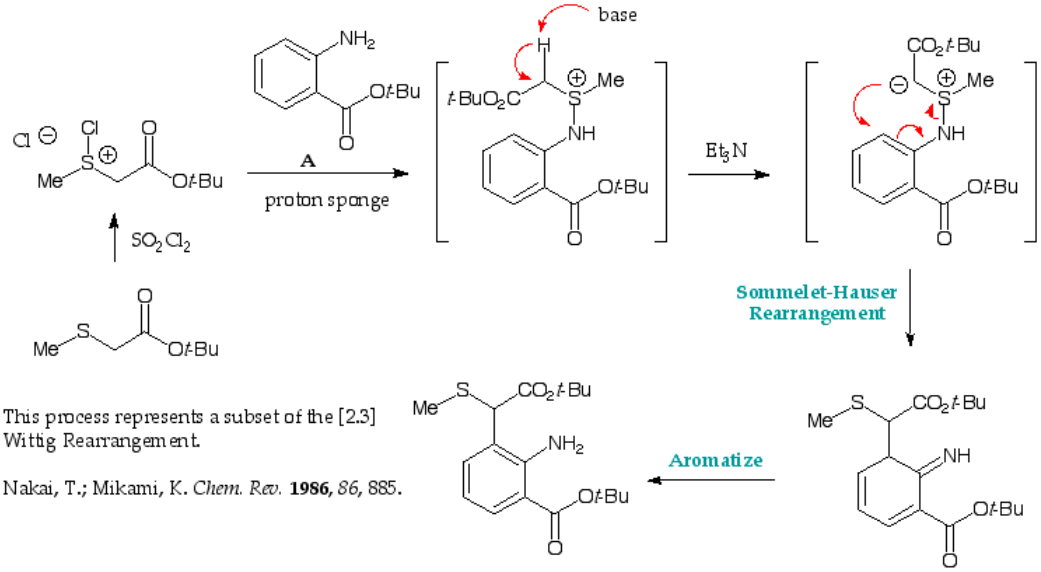
## Problem 284

Contributer: **Karl Scheidt**
Citation: *J. Org. Chem.* **1990**, *55*, 1374-1375

In 1990, Johnson reported the useful reaction illustrated below for the synthesis of *o*-aminophenylacetates (*J. Org. Chem.* **1990**, *55*, 1374). This general process is generalizable to the ortho alkylation of aniline derivatives.



Provide a plausible mechanism for this reaction.



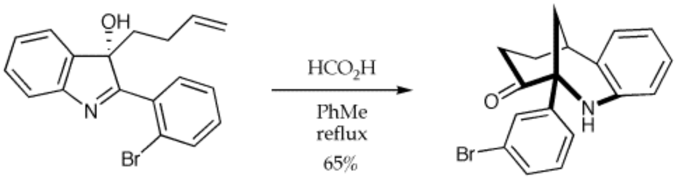
This process represents a subset of the [2,3] Wittig Rearrangement.

Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885.

## Problem 286

Contributer: **Keith Woerpel**
Citation: *Organic Lett.* **2003**, *5*, 333

McWhorter reported a transformation of indolenes that is likely involved in the biosynthesis of biologically active indole diterpenes (*Org. Lett* **2003**, *5*, 333). Provide a mechanism for the illustrated transformation.



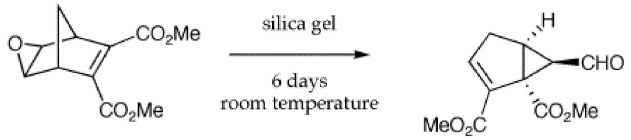
Provide a mechanism for the illustrated transformation.

---

The answer is provided in the paper.

**Problem 287** Contributer: **Keith Woerpel**
Citation: *J. Am. Chem. Soc.* **1994**, *116*, 3290

Provide a mechanism for the illustrated transformation, and rationalize the stereochemistry (S. Niwayama, S. Kobayashi *J. Am. Chem. Soc.* **1994,** *116,* 3290).



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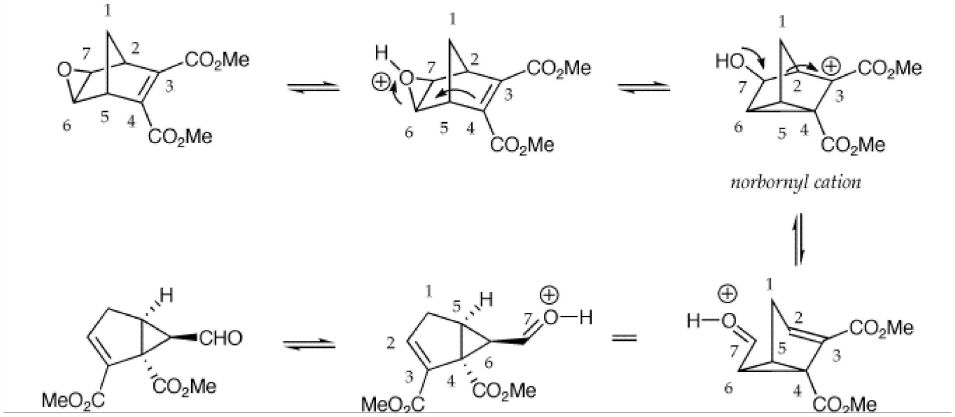
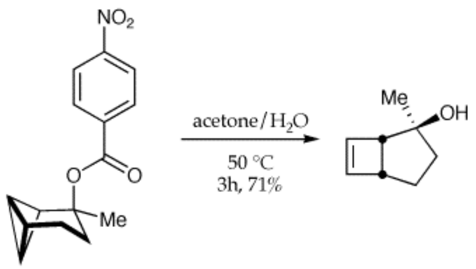


**Problem 289** Contributer: **Keith Woerpel**
Citation: *J. Org. Chem.* **1977**, *42*, 363

Provide a mechanism for the following transforrmation (K. Yano, K. Yoshida *J. Org. Chem.* **1977**, *42*, 363). The paper describes another related example as well as kinetic data for these reactions.



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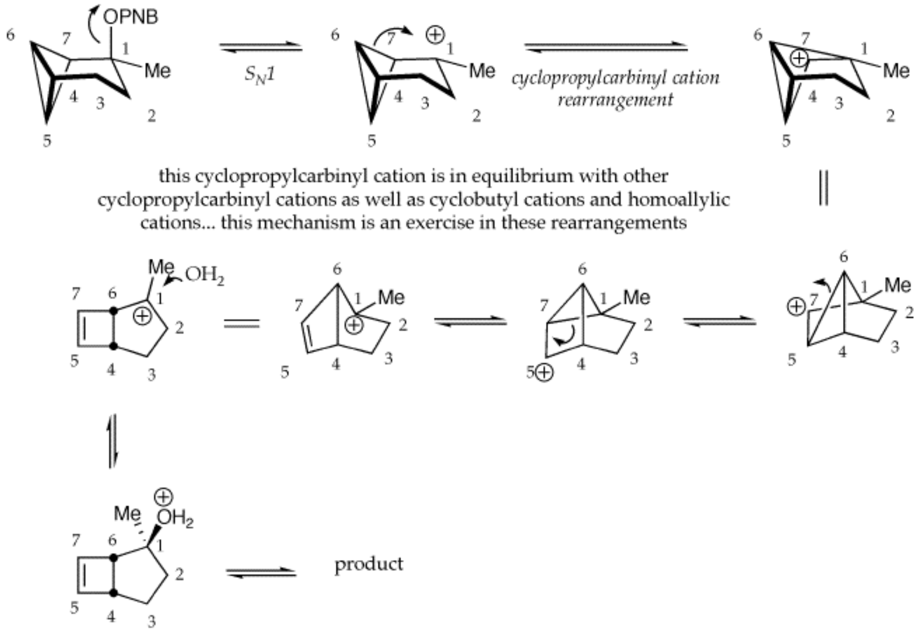
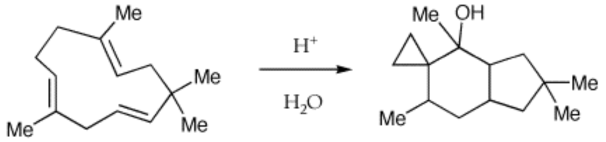
The paper offers one mechanism, but here is an alternative one that proceeds via a few more intermediates, thus avoiding a seemingly counterintuitive bond reorganization:



this cyclopropylcarbinyl cation is in equilibrium with other cyclopropylcarbinyl cations as well as cyclobutyl cations and homoallylic cations... this mechanism is an exercise in these rearrangements

**Problem 291** Contributer: **Keith Woerpel**
Citation: *Tetrahedron Lett.* **1995**, *36*, 1989

The biosynthesis of a family of sesquiterpenes, the pterosins, are believed to involve acid-catalyzed rearrangements. For example, the reaction shown below is believed to be part of the biosynthetic pathway. This transformation is part of Padwa's paper describing approaches to the synthesis of these natural products (A. Padwa *Tetrahedron Lett.* **1995**, *36*, 1989). Provide a mechanismfor this reaction.



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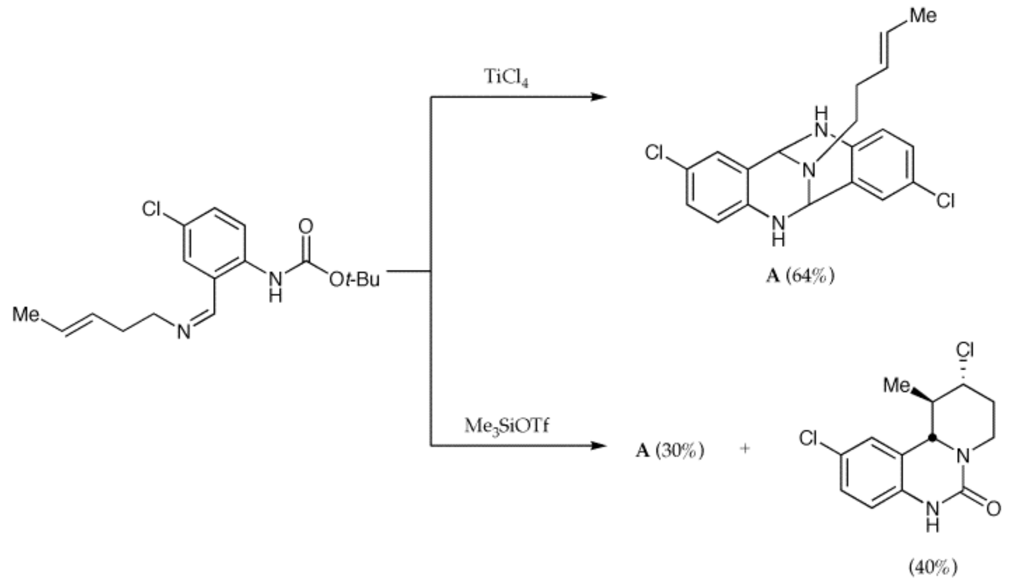
The mechanism is shown in the paper.

**Problem 292** Contributer: **Keith Woerpel**
Citation: *Tetrahedron Lett.* **1998**, *39*, 7239

Provide a mechanism for the following transformation (J. Aubé, *Tetrahedron Lett.* **1998**, *39*, 7239). Your mechanism should account for stereochemistry as well as the different outcomes depending upon Lewis acid.



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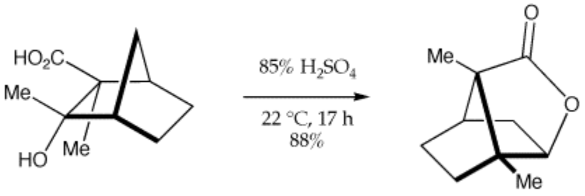
The mechanisms for these reactions are provided in the paper.

**Problem 295** Contributer: **Keith Woerpel**
Citation: *J. Org. Chem.* **1971**, *36*, 2324

Provide a mechanism for the following transformation (O. R. Rodig, *J. Org. Chem.* **1971**, *36*, 2324).



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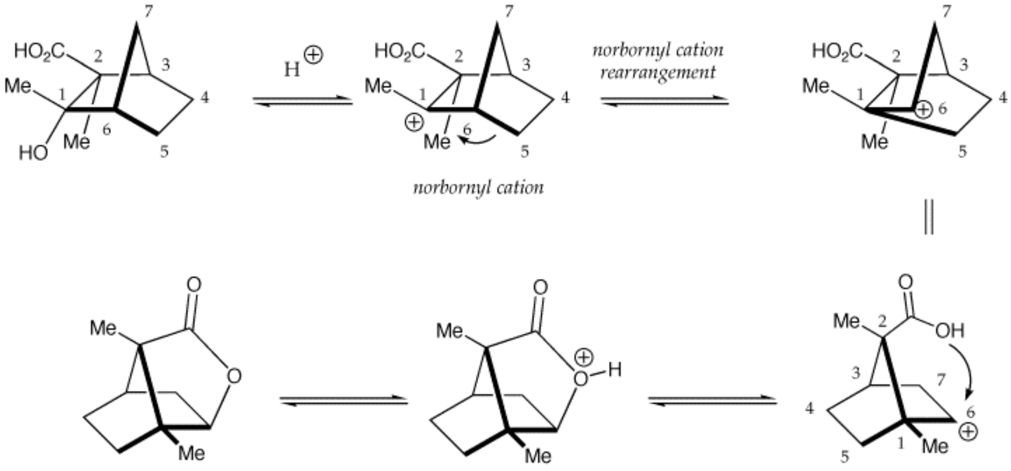
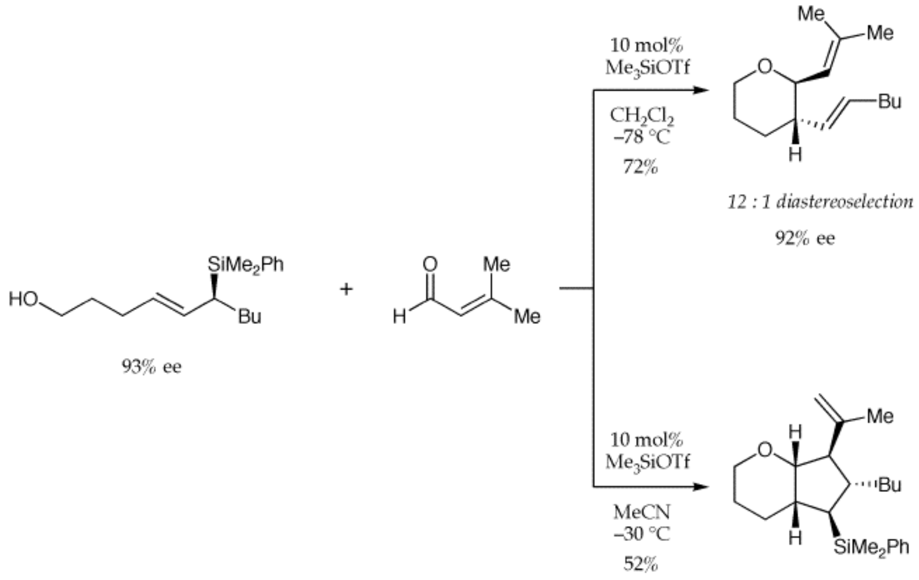


**Problem 296** Contributer: **Keith Woerpel**
Citation: *J. Org. Chem.* **1998**, *63*, 6096

Provide a mechanism for the following transformations (Y. Ito, *J. Org. Chem.* **1998**, *63*, 6096). Your answers should account for the stereochemistry of the reactions. This paper shows several other examples of the top reaction.

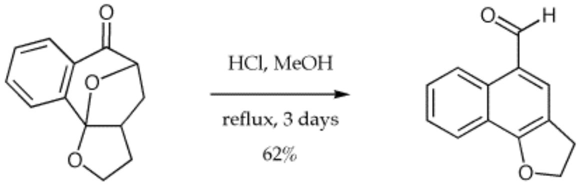


Mechanisms for these reactions are provided in the paper.

## Problem 298

Contributer: **Keith Woerpel**
Citation: *J. Am. Chem. Soc.* **1988**, *110*, 2894

Provide a mechanism for the following transformation (A. Padwa *J. Am. Chem. Soc.* **1988**, *110*, 2894).

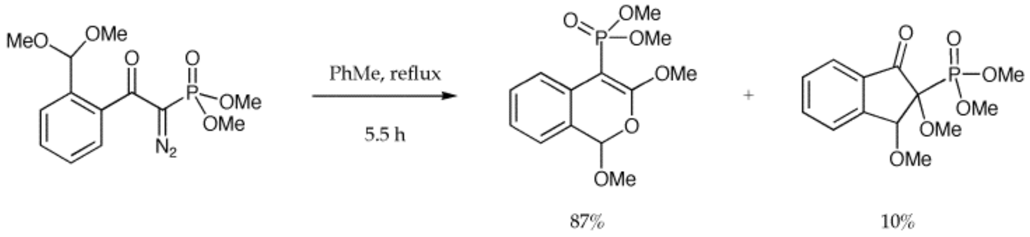


A mechanism is provided in the paper.

## Problem 299

Contributer: **Keith Woerpel**
Citation: *Tetrahedron* **1998**, *54*, 6457

Thermal decomposition of functionalized diazo compounds was found to provide some interesting structures (F. Léost, *Tetrahedron* **1998**, *54*, 6457). This paper includes several examples. Provide mechanisms for the formation of the following two products.

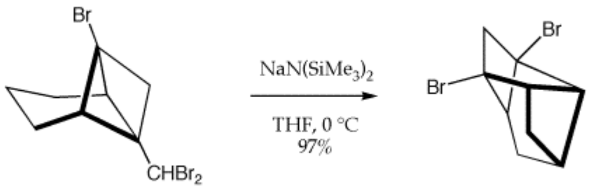


Mechanisms are provided in the paper.

## Problem 304

Contributer: **Keith Woerpel**
Citation: *J. Am. Chem. Soc.* **1999**, *121*, 7476

Provide a mechanism for the following transformation (G. Szeimies, *J. Am. Chem. Soc.* **1999,** *121*, 7476).



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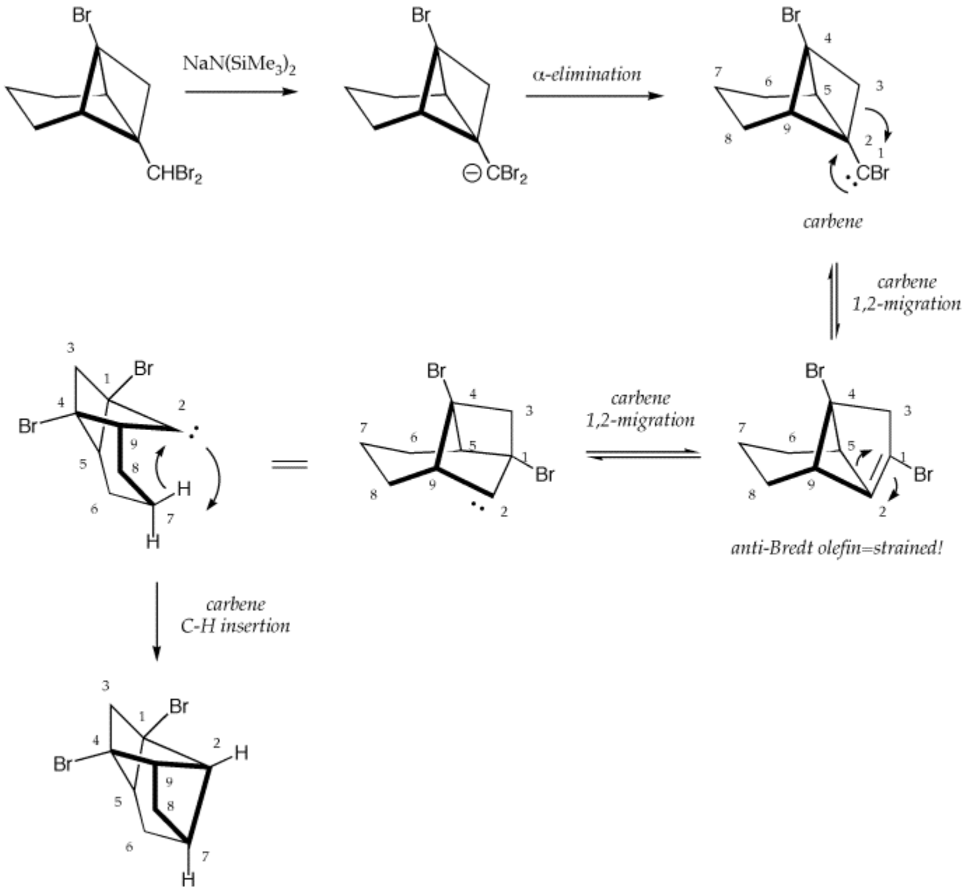
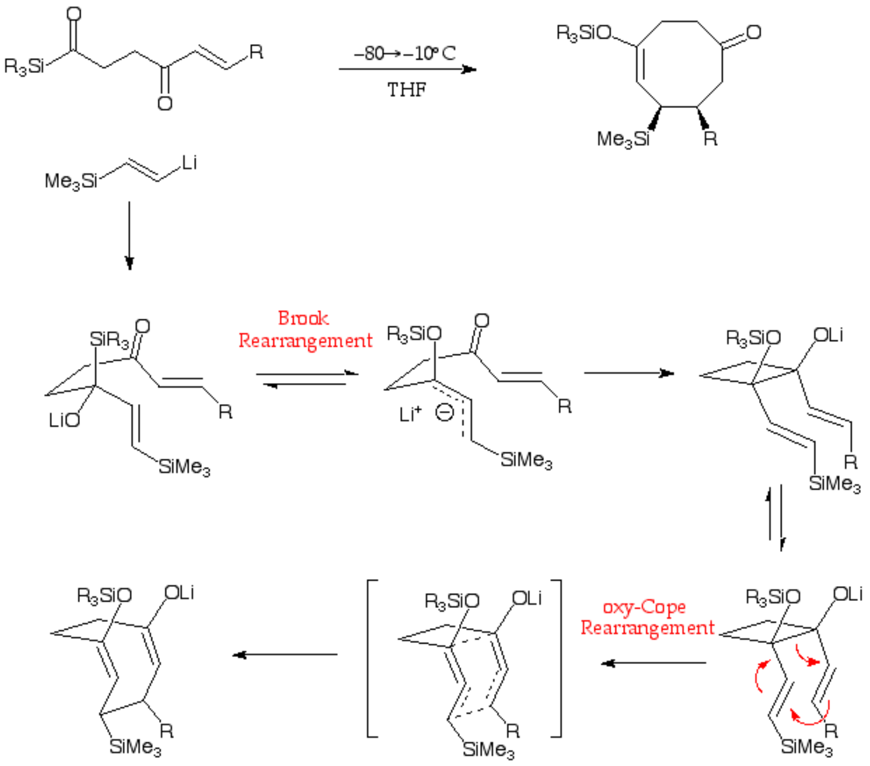


## Problem 305

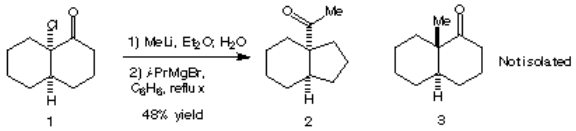
Contributer: **David A. Evans**
Citation: *Organic Lett.* **2003**, ASAP

A newly developed strategy has recently been reported for the construction of eight-membered rings (*Org. Lett.* **2003,** ASAP). Provide a plausible mechanism for the illustrated transformation. Please include conformational drawings that also explain the stereochemical outcome of the transformation.

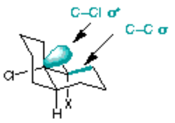


**Problem 310** Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1972**, *37*, 4090

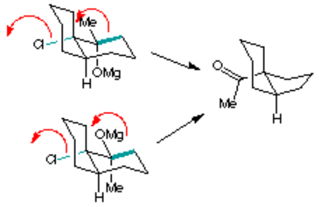
Sisti and Citale (*J. Org. Chem.* 1972, *37*, 4090) have reported that cis chlorodecalone (1) was treated with methyllithium and a mixture of stereoisomeric alcohols was isolated. When this mixture of alcohols was converted to the derived magnesium alkoxides and heated in benzene, the ring contracted product (2) was isolated in 48% overall yield. It is interesting that none of the trans methyldecalone (3) was observed.



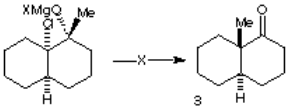
Part A. Rationalize the formation of 2 from both diastereomeric alcohols derived from 1. Please use carefully rendered three dimensional drawings to illustrate your answer.



the relevant migrating C–C bond aligns in an antiperiplanar arrangement with the antibonding C–Cl orbital in both instances

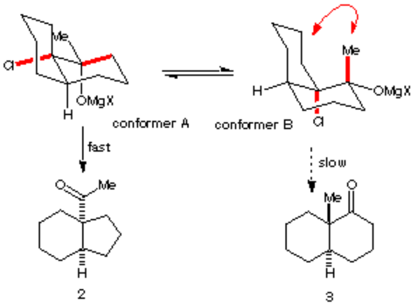


Part B. Explain why the indicated alkoxide does not lead to the formation of 3.



This alkoxide, in principle, could rearrange to give either reaction product. This point is illustrated in the appended scheme.

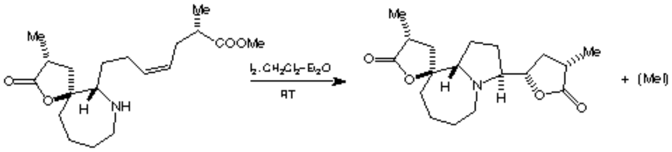
However, conformer B is strongly destabilized by the indicated double gauche pentane interaction. This destabilization is reflected in an increased activation energy for the rearrangement to 3. The rearrangement via conformer A to product 2 does not suffer such destabilization.



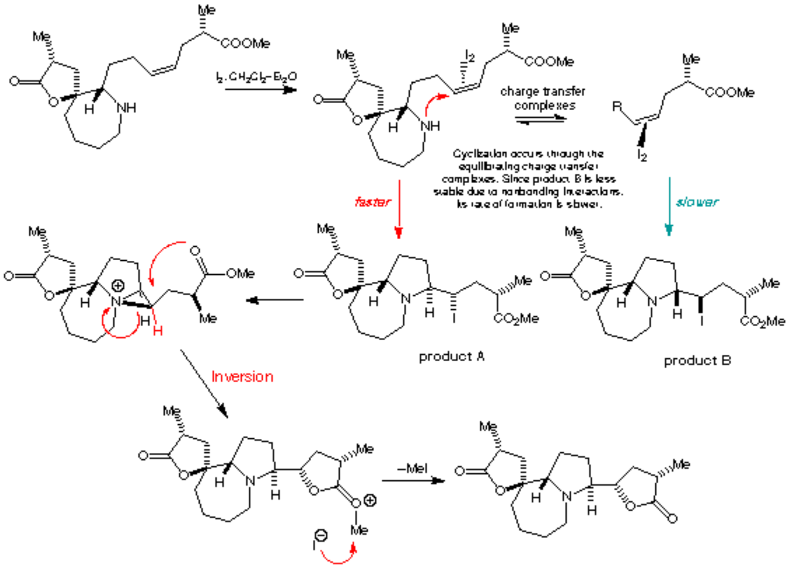
## Problem 311

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1986**, *111*, 1923

The iodine-induced transformation shown below is a key step in the Williams synthesis of croomine (*JACS* 1989, *111*, 1923). Given the stereochemical outcome of the illustrated transformation, propose a detailed mechanism for this reaction sequence. Williams has recently provided another closely reaction of the same design (*Org. Lett* 2003, *5*, 3361).



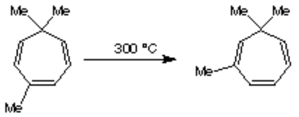
Answer


Me
Me
COOMe
O
O
H
NH
$I_2$, $CH_2Cl_2$–$Et_2O$
Me
$I_2$
COOMe
charge transfer complexes
R
$I_2$
Cyclization occurs through the equilibrating charge transfer complexes. Since product B is less stable due to nonbonding interactions, its rate of formation is slower.
faster
slower
Me
⊕
N
H
OMe
Me
Me
I
$CO_2Me$
product A
product B
Inversion
O⊕
Me
I⊖
–MeI

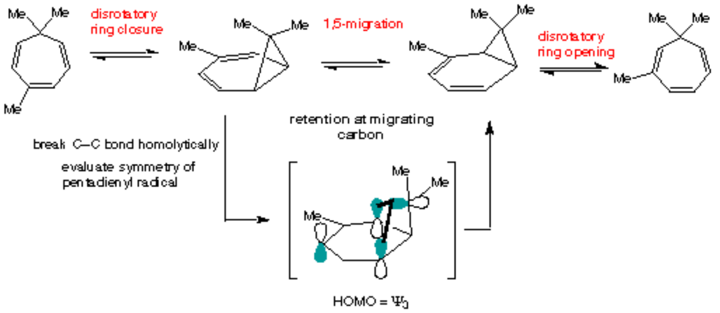
## Problem 315

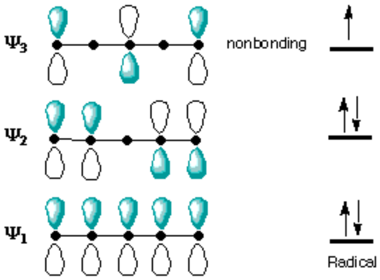
Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1966**, *88*, 2494

Berson and co-workers have studied the thermal isomerization illustrated below (*JACS* 1966, *88*, 2494-2502).



Provide a rationalization of these results. Three-dimensional drawings are recommended.

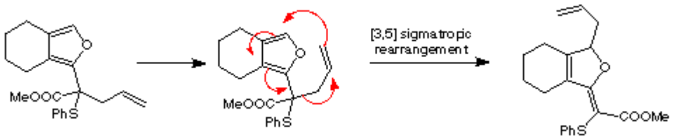




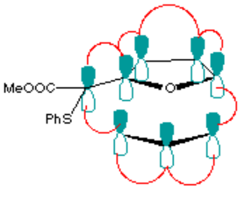
## Problem 325

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2003**, *5*, 2619

The furan shown below rearranges on standing at room temperature to the product shown below (*Org. Lett.* 2003, *5*, 2619). The mechanism proposed in the article for this transformation is a [3,5] sigmatropic rearrangement.



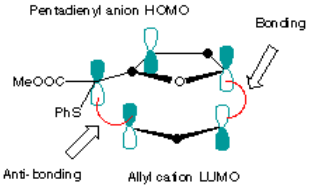
Part A. Please provide a Dewar-Zimmerman and an FMO analysis that illustrates why this is not a plausible mechanism.



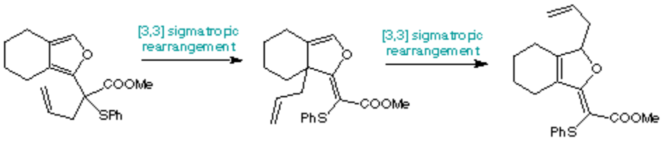
Dewar-Zimmerman Analysis
2 phase inversions
Huckel topology
8 electrons
Anti-aromatic and disallowed

FMO Analysis

Imagine breaking the fragments into a cation/anion pair (or a pair of radicals) and allow the HOMO and LUMO to interact.



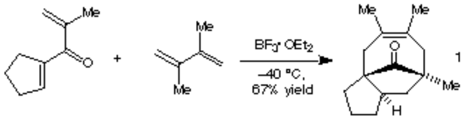
Part B. Please provide a mechanism for this rearrangement that is more consistent with the rules of orbital symmetry. You do not need to provide a justification for the step(s) of your mechanism.


O
COOMe
SPh
[3,3] sigmatropic rearrangement
O
PhS
COOMe
[3,3] sigmatropic rearrangement
O
PhS
COOMe

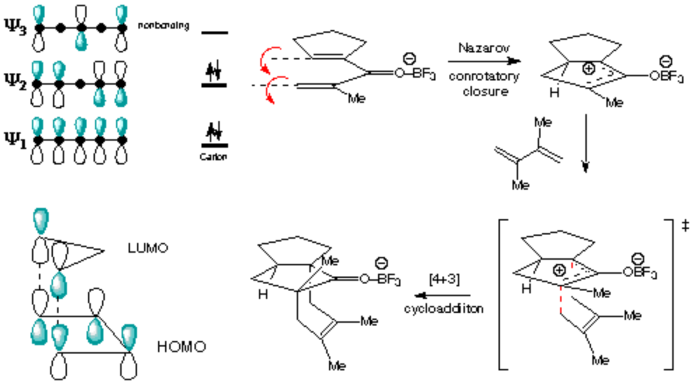
## Problem 326

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2003**, *5*, 2747-2750

The illustrated transformation reported this year by West and co-workers (*Org. Lett.* 2003, *5*, 2747-2750) rapidly facilitates the construction of the complex tricyclic ketone 1 in 67% yield.



Please provide a concise mechanism for this transformation. Use 3-dimensional representations where appropriate to illustrate your answer.

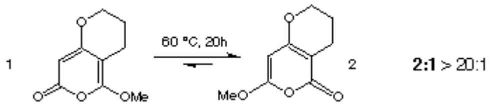


The cycloaddition

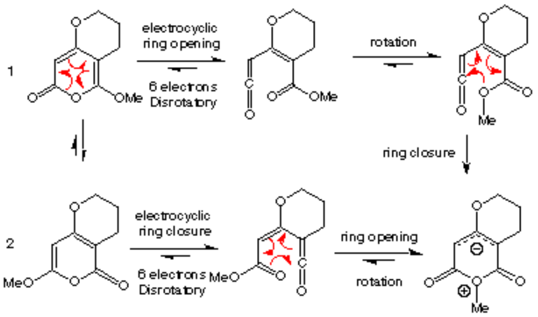
## Problem 327

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1989**, *30*, 3509-3512

In 1989, Cha reported a study on the thermal isomerization of alkoxypyrones (*Tet. Lett.* 1989, *30*, 3509-3512). One of the cases studies was the rearrangement of 1→2.

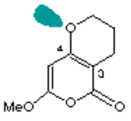


Part A. Provide a mechanism for this rearrangement in the space below.



Part B. At equilibrium, 2 is strongly favored over 1 (2:1 >20:1). Please rationalize product stability on the basis of the anomeric effect as was done by the authors.

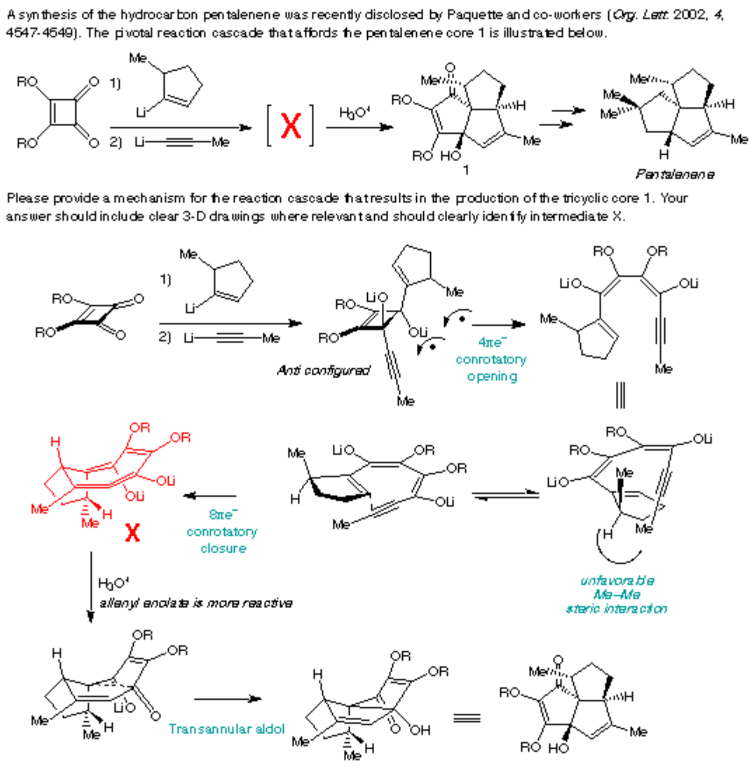
The authors suggest that the added anomeric effect of the indicated oxygen lone pair donating into the polarized σ* C–C 3-4 is consistent with the noted the difference in stability



2

## Problem 328

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2002**, *4*, 4547-4549



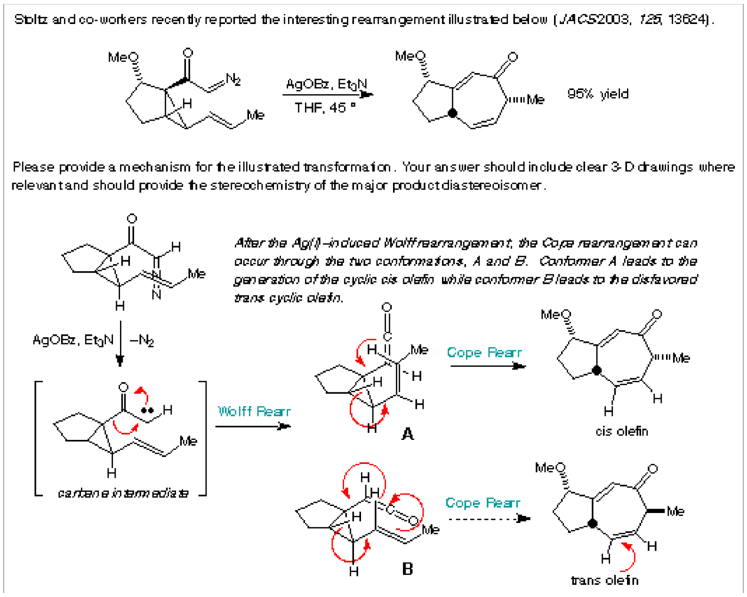
A synthesis of the hydrocarbon pentalenene was recently disclosed by Paquette and co-workers (*Org. Lett.* 2002, *4*, 4547-4549). The pivotal reaction cascade that affords the pentalenene core 1 is illustrated below.

Please provide a mechanism for the reaction cascade that results in the production of the tricyclic core 1. Your answer should include clear 3-D drawings where relevant and should clearly identify intermediate X.

RO
1)
Me
Li
2) Li—≡—Me
[ X ]
$H_3O^+$
RO
HO
1
Pentalenene
Anti configured
$4\pi e^-$ conrotatory opening
LiO
OLi
OR
X
$8\pi e^-$ conrotatory closure
unfavorable Me–Me steric interaction
$H_3O^+$
*allenyl enolate is more reactive*
Transannular aldol
OH

## Problem 332

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2003**, *125*, 13624-13625



Stoltz and co-workers recently reported the interesting rearrangement illustrated below (*JACS* 2003, *125*, 13624).

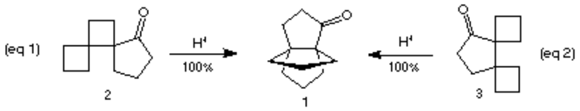
Please provide a mechanism for the illustrated transformation. Your answer should include clear 3-D drawings where relevant and should provide the stereochemistry of the major product diastereoisomer.

*After the Ag(I)–induced Wolff rearrangement, the Cope rearrangement can occur through the two conformations, A and B. Conformer A leads to the generation of the cyclic cis olefin while conformer B leads to the disfavored trans cyclic olefin.*

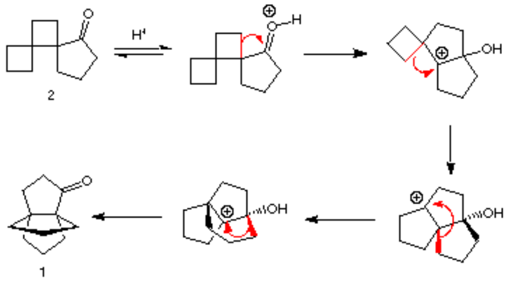
## Problem 335

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1985**, *26*, 5277-5280

Fitjer and co-workers (*Tet. Lett.* 1988, *29*, 263) have reported a very interesting approach to the [3,3,3]propellane 1. This tricyclic ketone may be produced in quantitative yield through acid-catalyzed rearrangement of ketones 2 or 3.



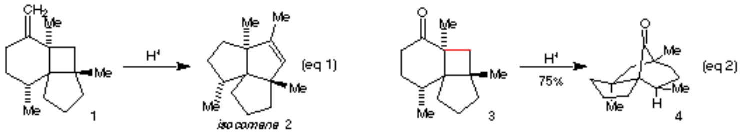
Please provide a plausible mechanism for the rearrangement 2→1 (eq 1). Use 3-dimensional representations where appropriate to illustrate your answer.



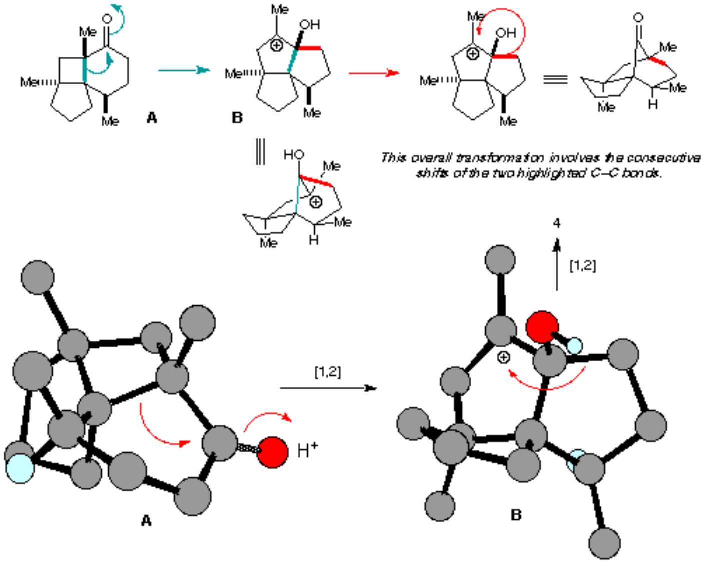
## Problem 336

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1982**, *103*, 82-87

We have discussed the Pirrung approach to the synthesis of isocomene (2) (*JACS* 1982, *103*, 82-87) that features the acid catalyzed rearrangement illustrated below (eq 1). In the Pirrung study the rearrangement of ketone 3 was also reported (eq 2).



Please provide a plausible mechanism for the rearrangement 3→4 (eq 2). Use 3-dimensional representations where appropriate to illustrate your answer.

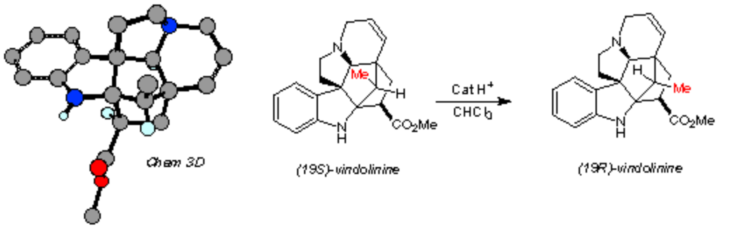


*This overall transformation involves the consecutive shifts of the two highlighted C–C bonds.*

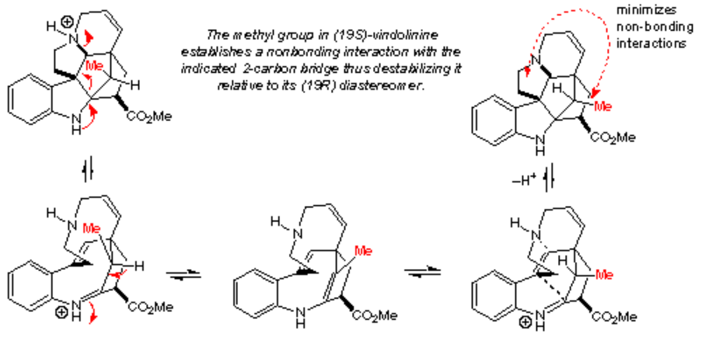
## Problem 338

Contributer: **David A. Evans**
Citation: *Z. Naturforsch* **1986**, 386

The indole alkaloid *(19S)*-vindolinine readily isomerizes into its (*19R*) diastereomer under the influence of trace amounts of acid present in chloroform (Atta-ur-Rahman Z. *Naturforsch* 1986, 386).



Provide a mechanism for this rearrangement in the space below. Explain why (19R) isomer is more stable than (19S).

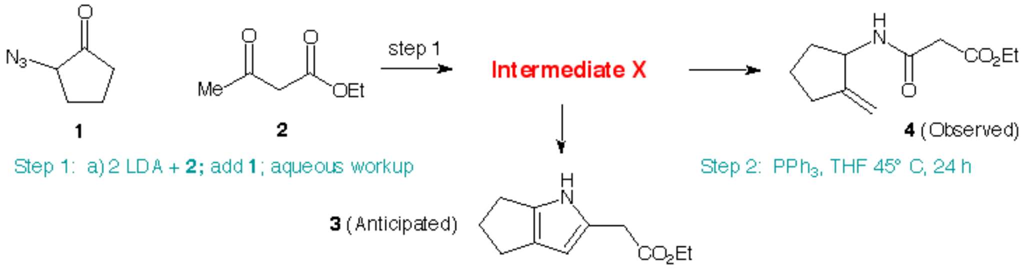


*The methyl group in (19S)-vindolinine establishes a nonbonding interaction with the indicated 2-carbon bridge thus destabilizing it relative to its (19R) diastereomer.*

## Problem 343

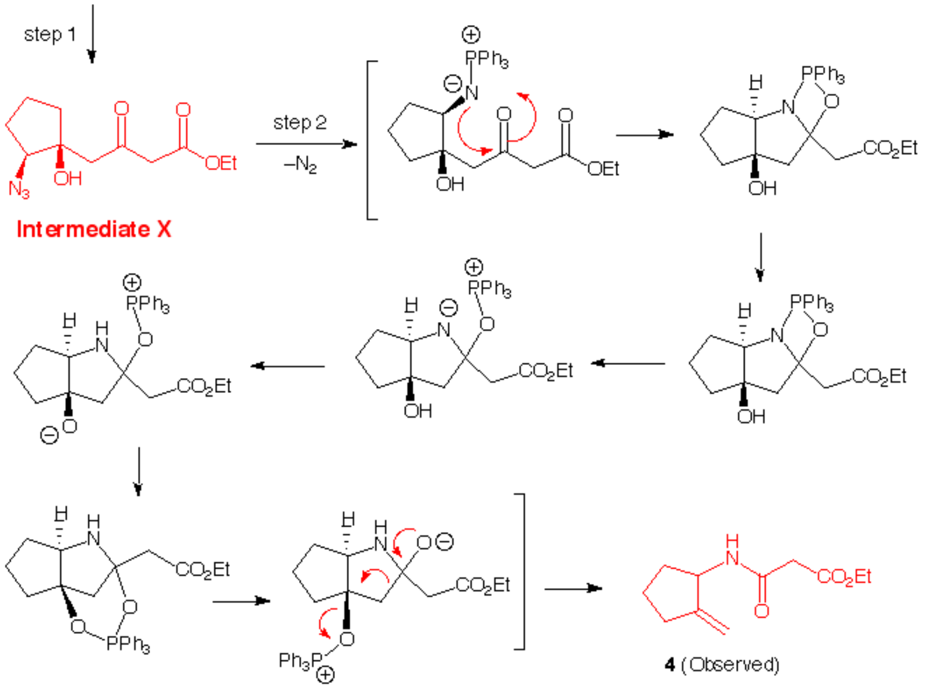
Contributer: **David A. Evans**
Citation: *Chem. Commun.* **2003**, 3044

Langer and co-workers recently reported the interesting *errant* Staudinger reaction illustrated below ( *Chem Comm.* **2003**, 3044). The anticipated reaction product was pyrrole **3** while the observed product was **4**.

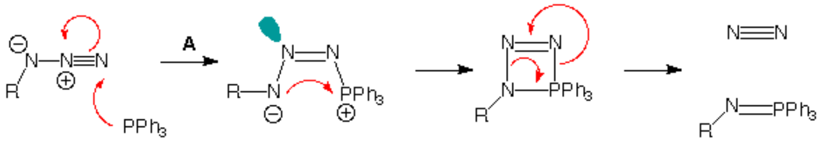


1
2
step 1
Intermediate X
3 (Anticipated)
4 (Observed)
Step 1: a) 2 LDA + 2; add 1; aqueous workup
Step 2: PPh3, THF 45° C, 24 h

Provide a detailed mechanism for this transformation.



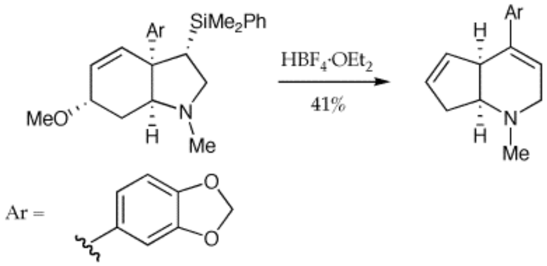
**Mechanism of the Staudinger Reaction**



In Step A, nucleophiles perferentially add to azides to give an intermediate having the cis geometry as shown as documented by Trost (*JACS* **1983**, *105*, 1054) for Grignard reagents. A stereoelectronic argument may be used to account for the cis stereoselection.

**Problem 344** Contributer: **Keith Woerpel**
Citation: *J. Org. Chem.* **1994**, *59*, 5662

As part of a planned synthesis of an *Amaryllidaceae* alkaloid, Pearson and Postich attempted a Tamao-Fleming oxidation, but a rearranged product was obtained. Provide a mechanism for the following transformation (W. H. Pearson, M. J. Postich, *J. Org. Chem.* **1994**, *59*, 5662).



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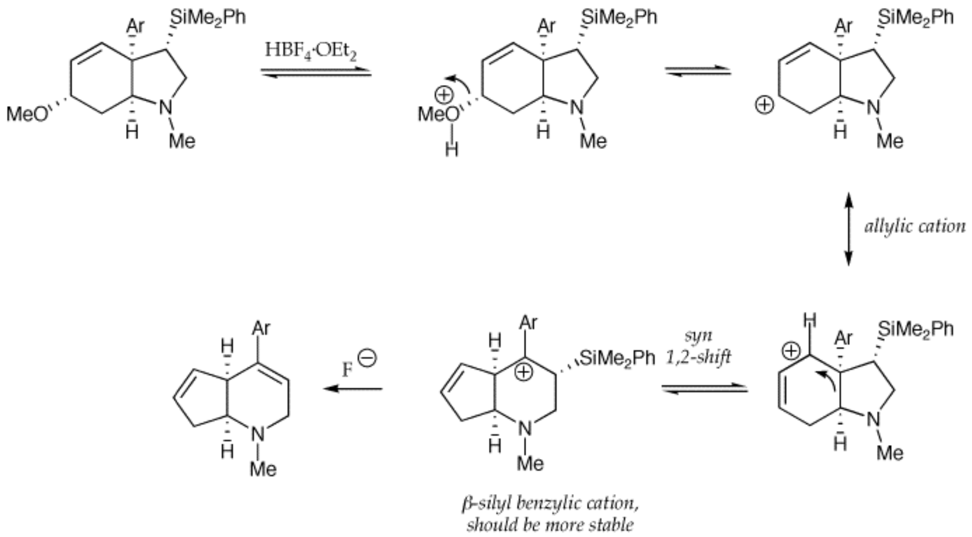
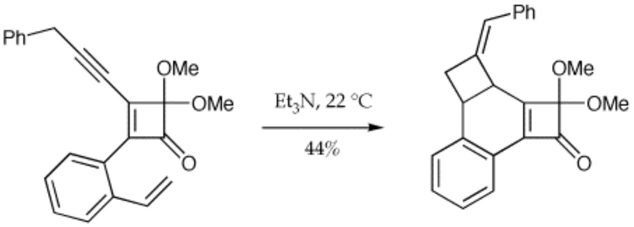
While the paper provides a mechanism, an alternative involving more intermediates may also be feasible.



**Problem 346** Contributer: **Keith Woerpel**
Citation: *J. Org. Chem.* **2002**, *67*, 1388

Provide a mechanism for the following transformation (A. R. Hergueta, H. W. Moore, *J. Org. Chem.* **2002**, *67*, 1388).



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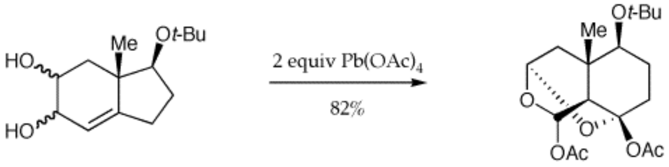
A mechanism is provided in the paper.

**Problem 347** Contributer: **Keith Woerpel**
Citation: *J. Org. Chem.* **2002**, *67*, 2447

Provide a mechanism for the following transformation (C. Unaleroglu, V. Aviyente, S. Arseniyadis, *J. Org. Chem.* **2002**, *67*, 2447).



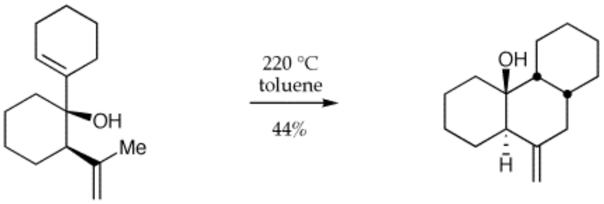
---

A mechanism is provided in the paper.

## Problem 349

Contributer: **Keith Woerpel**
Citation: *Organic Lett.* **2000**, *2*, 663

Thermolysis of 1,2-divinylcyclohexanols leads to some interesting products (J. M. Warrington, G. P. A. Yap, L. Barriault, *Org. Lett.* **2000**, 2, 663). Provide a mechanism for this reaction, including a rationalization of stereochemistry.



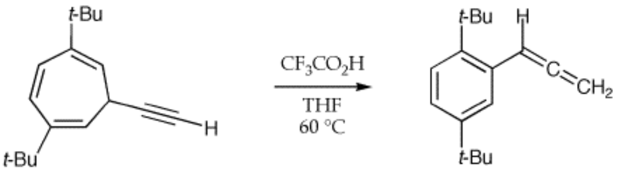
---

A mechanism and an explanation of the stereochemistry is provided in the paper.

## Problem 353

Contributer: **Keith Woerpel**
Citation: *Organic Lett.* **2000**, *2*, 3011

Provide a mechanism for the following reaction (T. Kitagawa, *Org. Lett.* **2000**, 2, 3011).



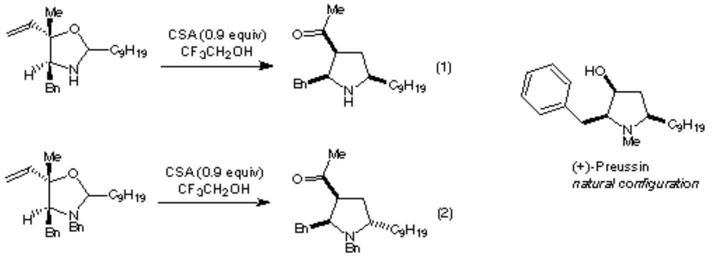
---

A mechanism is provided in the paper.

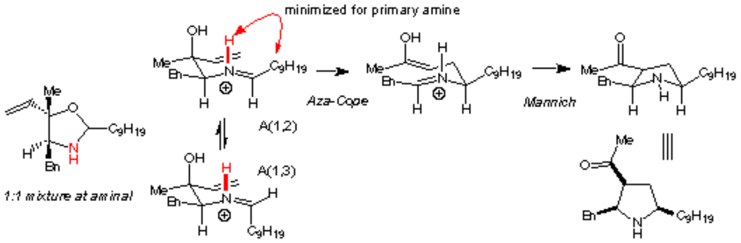
## Problem 359

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.*

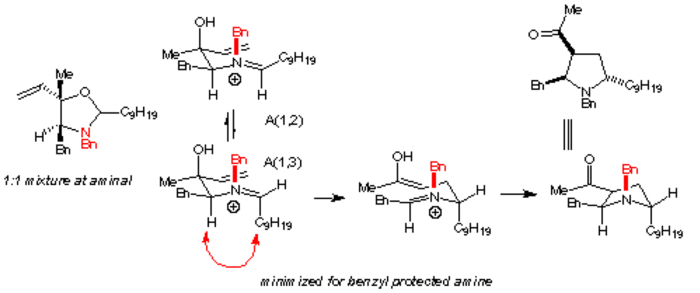
An elegant enantiodivergent synthesis of the potent anti-fungal reagent Preussin was reported by Overman (*JACS* 1994, 11241.).



Part A. Provide a mechanism for the transformation illustrated in Eq 1. Where stereochemicasl issues are involved, 3-dimensional drawings should be employed.



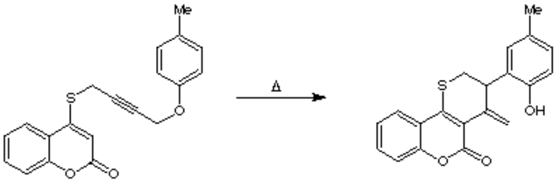
Part B. Provide a mechanism for the transformation illustrated in Eq 2. Where stereochemicasl issues are involved, 3-dimensional drawings should be employed.

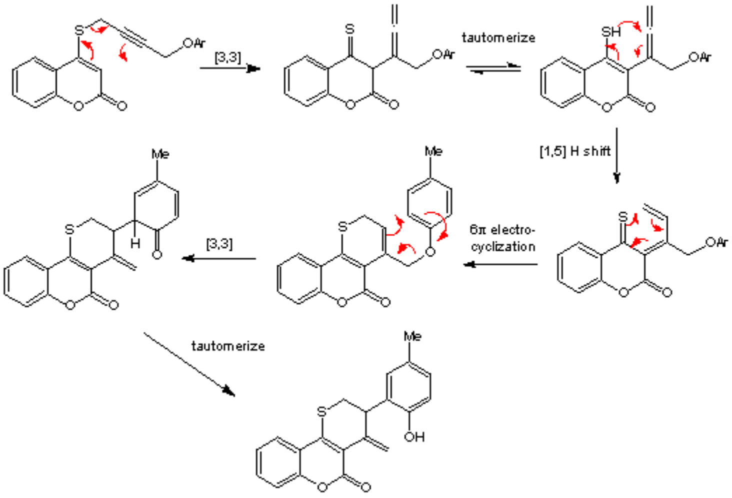


## Problem 364

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2002**, *4*, 2629

A recent paper by Majumdar and co-workers reported the transformation illustrated below (*Organic Lett* 2002, *4*, 2629). Please provide a mechanism for this process. Feel free to use trace quantities of HX when needed.

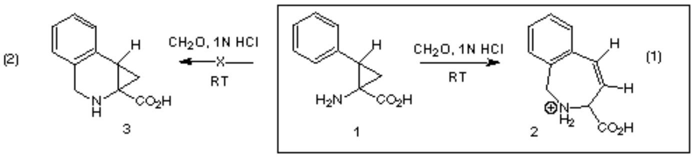


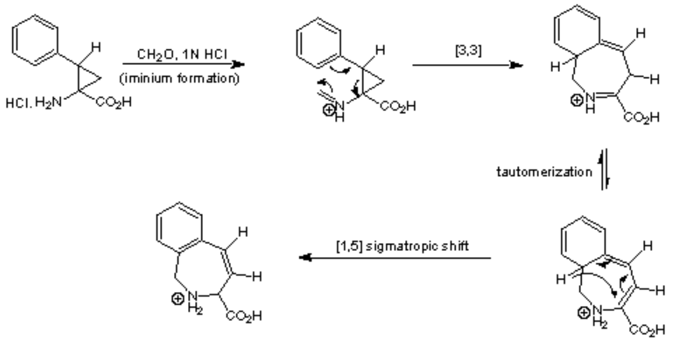


## Problem 365

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2001**, *66*, 2884

A recent paper by Martens (*JOC* 2001, *66*, 2884) reported the reaction shown below (Eq 1). Please provide a mechanism for the conversion of 1 to 2. It is noteworthy that the Pictet-Spengler of 1 does not give 3.

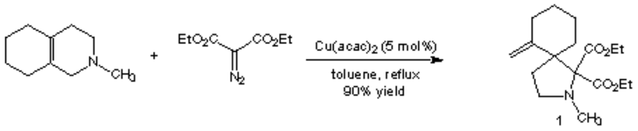


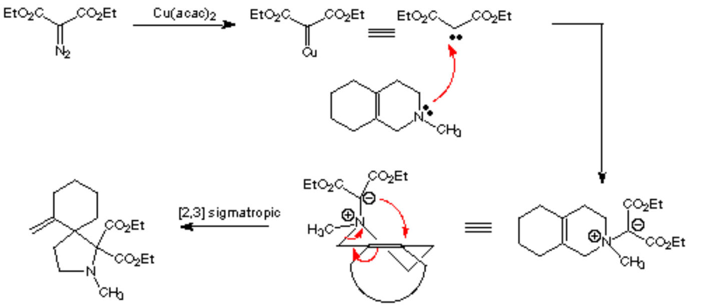


## Problem 367

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2003**, *5*, 4775

A recent paper by Workman and co-workers (*Org. Lett.* 2003, *5*, 4775) describe an efficient reaction for the formation of spiro-heterocycle 1. Propose a mechanism for the formation of 1.

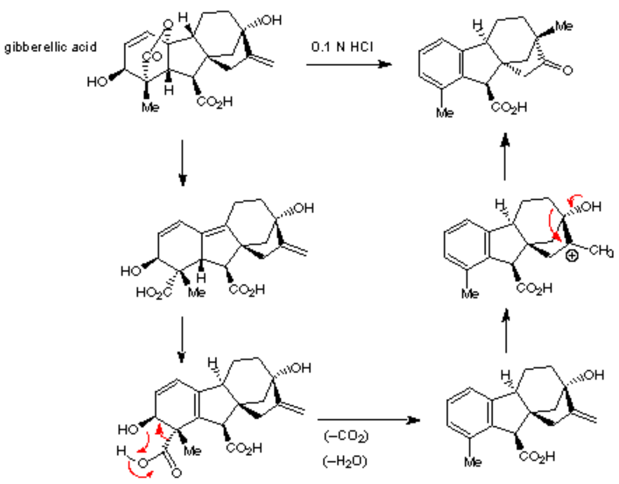




## Problem 370

Contributer: **Jonathan scheerer**
Citation:

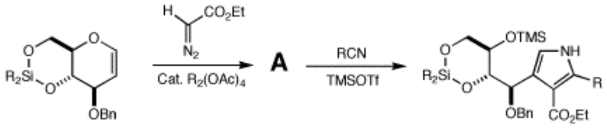
Gibberellic acid is a notoriously sensitive natural product. Rearrangement occurs readily in both acidic and basic conditions. Provide a mechanism for the illustrated rearrangement under dilute HCl.



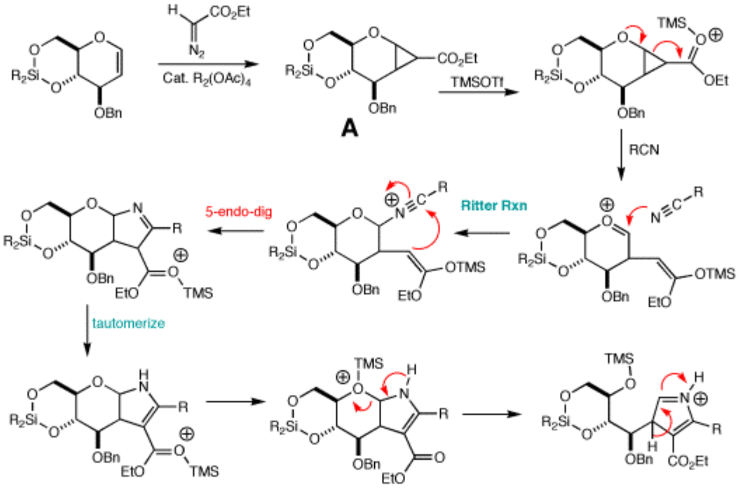
## Problem 374

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2003**, *5*, 5099

Pagenkopf and Yu have recently reported a new "diversity-oriented" synthesis of pyrroles (*Org. Lett.* **2003**, *5*, 5099). The two-step process illustrated below will accomodate a range of "R" substituents.



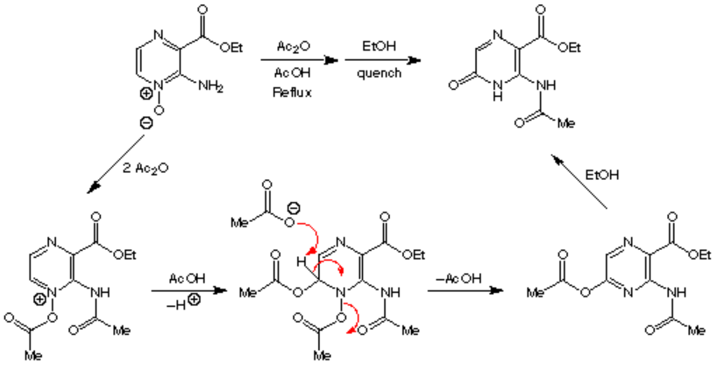
Provide a mechanism for the overall process and clearly identify intermediate **A**.



## Problem 376

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1975**, 2431

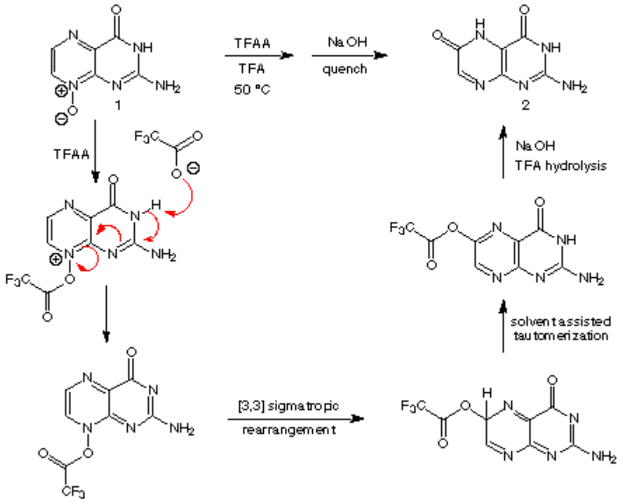
The Katada rearrangement is a method to effect site specific oxidation of certain aromatic heterocycles. Please provide a mechanism for the specific example of the Katada rearrangement shown below (*J. Org. Chem.* 1975, 2431).



## Problem 377

Contributer: **Travis Dunn**
Citation: *J. Org. Chem.* **1975**, 2431

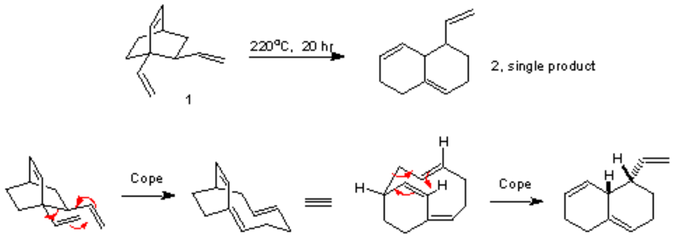
The Katada rearrangement is a method to effect site specific oxidation of certain aromatic heterocycles. Please provide a mechanism for the specific example of the Katada rearrangement shown below (*J. Org. Chem.* 1975, 2431). When heterocycle 1 was treated with warm trifluoroacetic anhydride and trifluoroacetic acid, the unexpected product 2 was isolated. Please provide a mechanism for this unusual rearrangement.



## Problem 378

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1994**, *116*, 1776

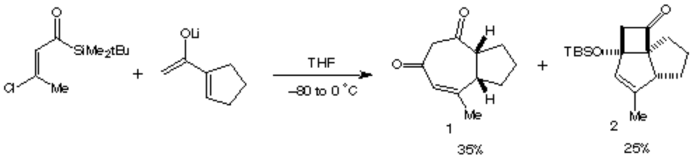
Paquette and co-workers have reported that thermal isomerization of 1 occurs to give triene 2 as a single diastereomer (*JACS* 1994, *116*, 1776). Provide a plausible mechanism for this transformation and provide the product stereochelmical relationship of 2 based on the absolute stereochlemistry of the starting triene 1.



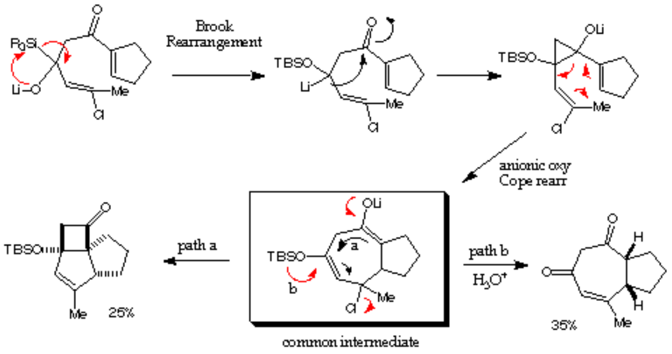
## Problem 380

Contributer: **David A. Evans**
Citation: *Organic Lett.* **1999**, 677

Takeda and co-workers have developed an efficient strategy for the synthesis of fused 5,7 ring systems by reacting acylsilanes with lithium enolates (*Org. Lett.* 1999, 677). Although the 5,7 bicyclic product 1 is often observed, the nature of the enolate nucleophile can affect the course of the reaction.



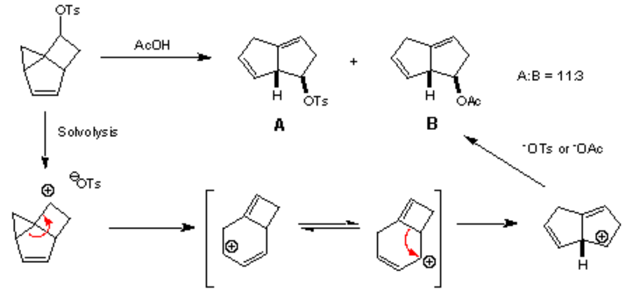
Provide a mechanism for the formation of both the anticipated 5,7 bicycle 1 and the tricyclic ketone 2.



## Problem 383

Contributer: **David A. Evans**
Citation: *Tetrahedron* **2000**, *56*, 2591

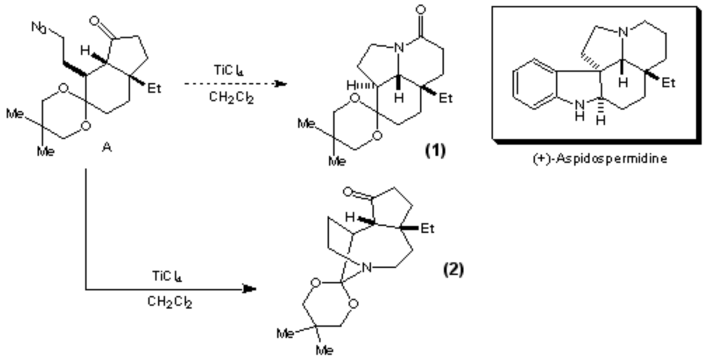
Kass has reported the interesting carbonium ion rearrangement shown below (*Tetrahedron*, 2000, *56*, 2591). Provide a mechanism for this transformation.

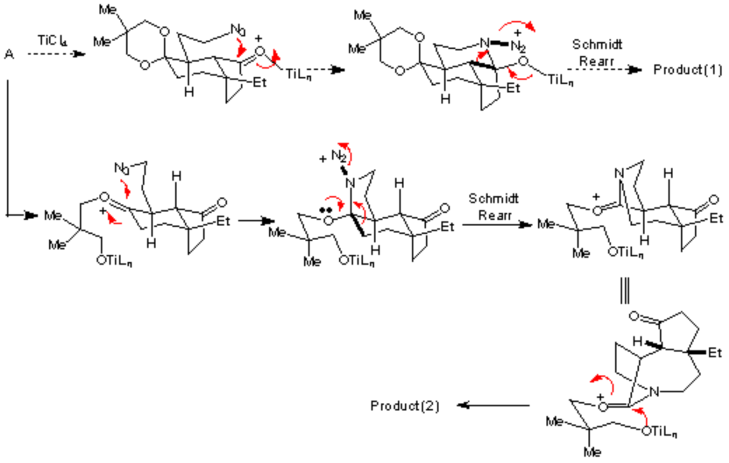


## Problem 384

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2000**, 1625

A key step in Aube's total synthesis of (+)-Aspidospermidine (*Org. Lett.*, 2000, 1625) involved the rearrangement shown in equation (1) to form the requisite nitrogen heterocycle. However, upon subjection of the starting azide to Lewis acidic conditions, an unexpected rearrangement occurred as shown in equation (2). Provide a mechanism for the formation of both the expected and unexpected products.





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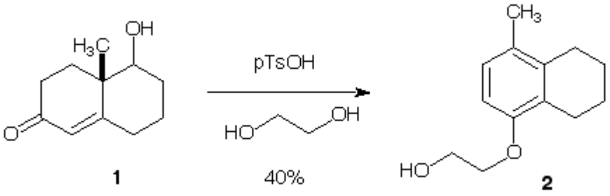
## Problem Answers

### Problem 387

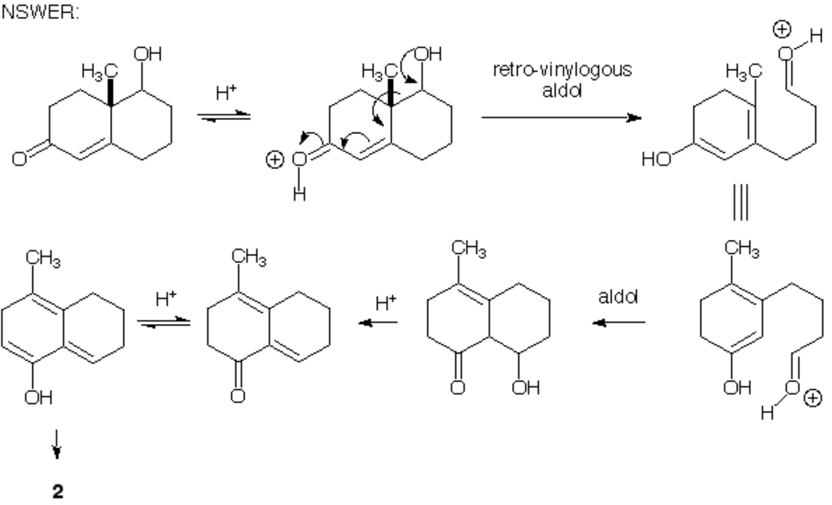
Contributer: **Karl Scheidt**
Citation: *Tetrahedron Lett.* **1965**, *21*, 2297

The formation of ketals from ketones is usually a straightforward operation. However, it was found that treatment of unsaturated ketone **1** with pTsOH and ethylene glycol did not provide the expected ketal, but the aromatic compound **2** as the major product (Tetrahedron Lett. **1965**, *21*, 2297).



Provide a plausible mechanism for this reaction.

ANSWER:



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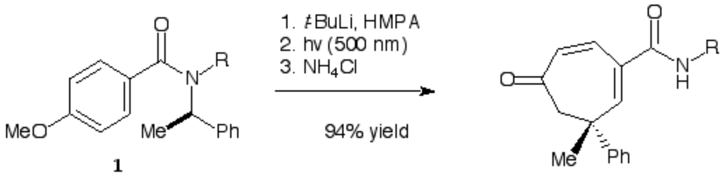
## Problem Answers

### Problem 391

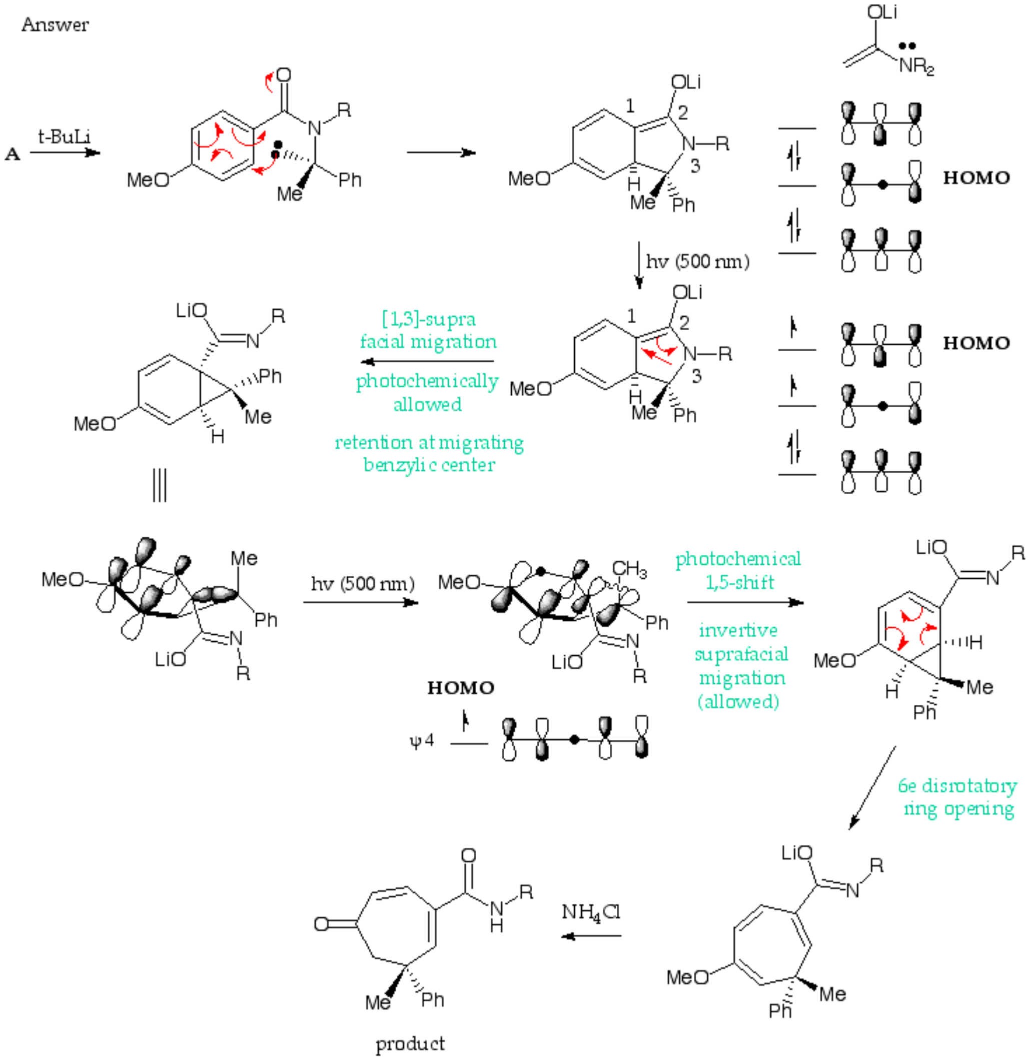
Contributer: **Karl Scheidt**
Citation: *J. Am. Chem. Soc.* **2003**, *125*, 9278

A recent approach to the construction of 7-membered rings from aromatic systems such as **1** involves the following sequence of reactions (J. P. Clayden; F. E. Knowles & C. J. Menet *J. Am. Chem. Soc.* **2003** *125*, 9278-9279).



Propose a mechanism for this reaction and pay careful attention to any sigmatropic and pericyclic processess.

Answer



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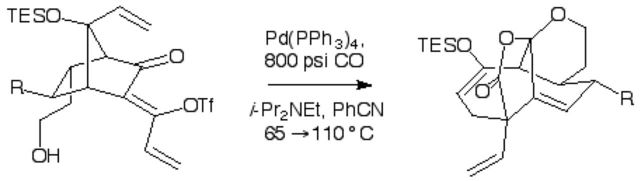
## Problem Answers

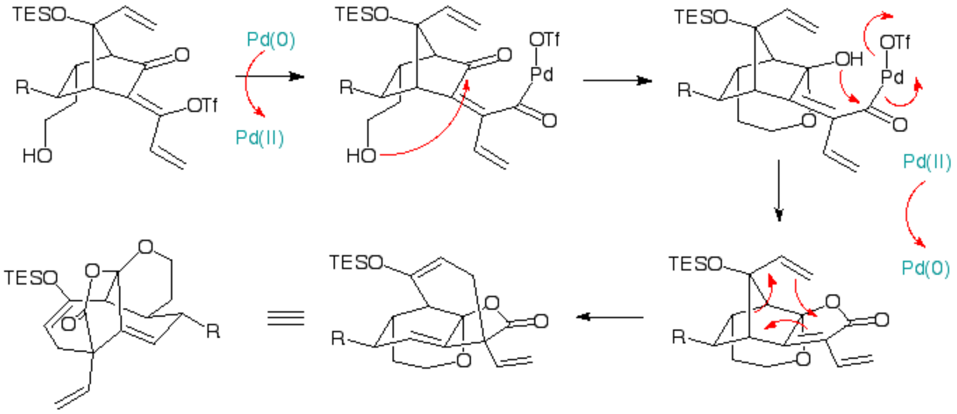
### Problem 404

Contributer: **Phillip S. Baran**
Citation: *Organic Lett.* **2000**, *2*, 2905

Leighton and Bio have recently disclosed the following approach to the core of CP-263,114 ( *Org. Lett* **2000**, 2905).



Please provide a mechanism for this transformation.



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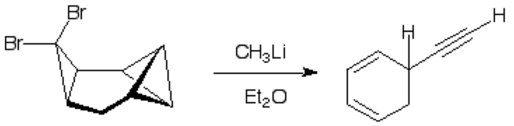
## Problem Answers

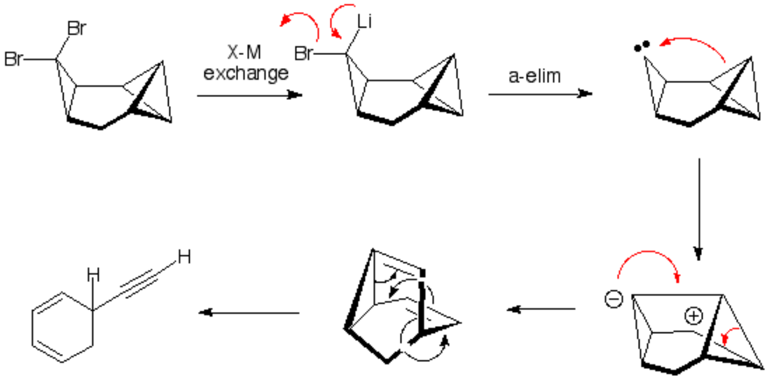
### Problem 405

Contributer: **Phillip S. Baran**
Citation: *Angew. Chem.* **1975**, 765

Lechner and Christl described this interesting, albeit unintended degradation of **1** upon treatment with methyllithium (*Angew. Chem. Int. Ed.* **1975**, 765). These studies were undertaken en route to tetrahedrane, although the ultimate goal was never realized.



Please provide a mechanism for this transformation.



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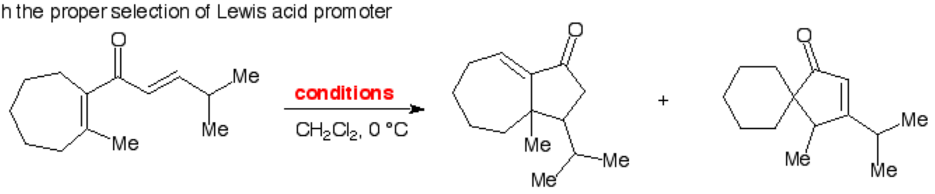
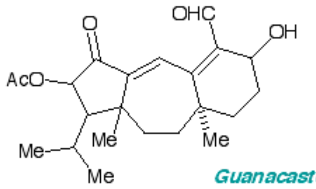
## Problem Answers

### Problem 407

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2004**, *6*, 613

Chiu and Li have reported the illustrated acid-promoted cyclization that was designed to serve as a pivotal bond construction in the synthesis of guanacastepene A (*Org. Lett* **2004**, *6*, 613). The authors note that the principal products may be regulated through the proper selection of Lewis acid promoter

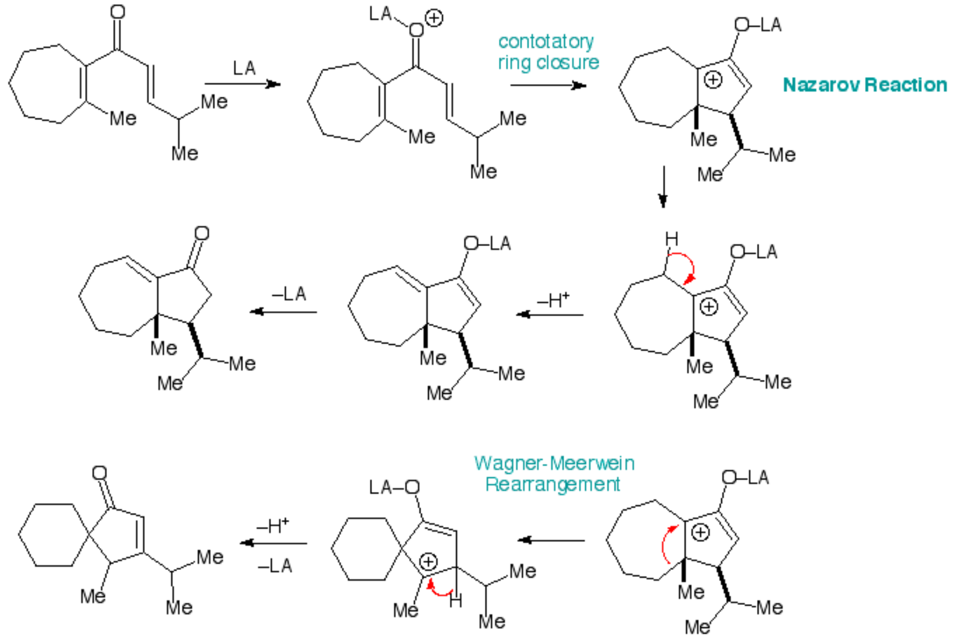




*Guanacastepene A*

| conditions | ratio | yield |
|---|---|---|
| $BF_3 \cdot OEt_2$ | >95:05 | 98% |
| $BCl_3$ | 05:95 | 92% |

Provide a detailed mechanism for the formation of both products. Please denote the anticipated relative stereochemical relationship for the hydroazulane product.



For an excellent overview of the Nazarov reaction see: Habermas, K. L.; Denmark, S. E.; Jones, T. K. "The Nazarov Cyclization." *Org. React. (N. Y.)* **1994**, *45*, 1-158.

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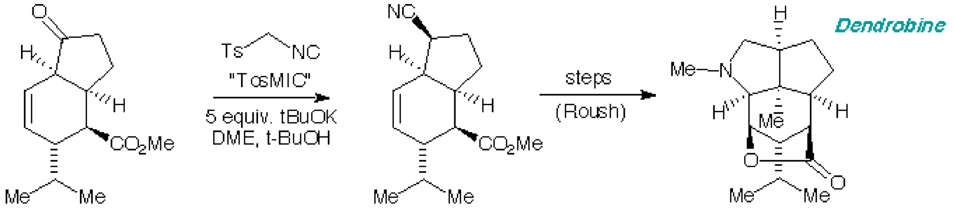
## Problem Answers

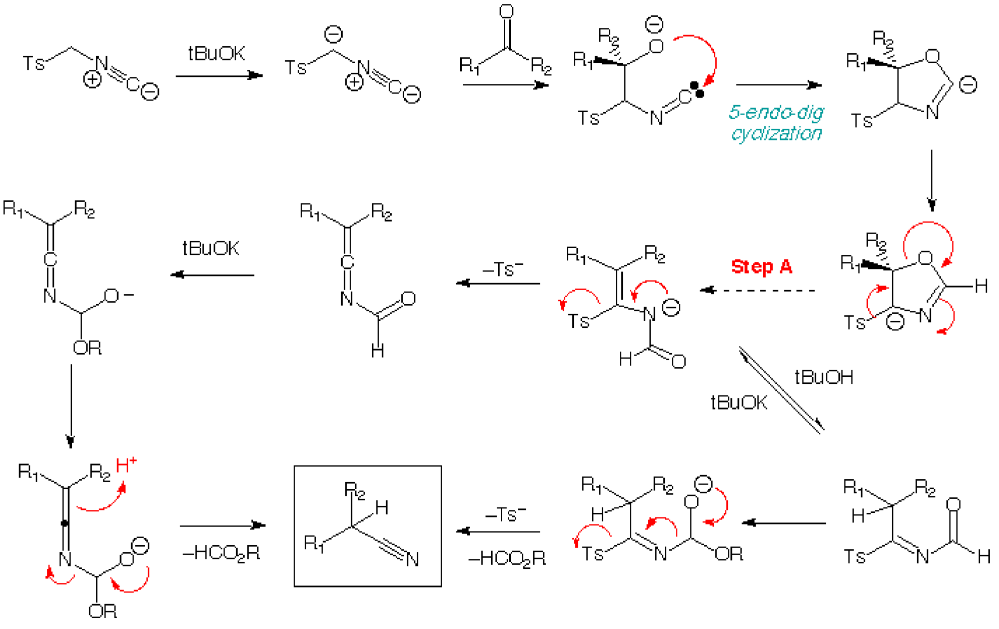
### Problem 409

Contributer: **Dan O,Malley**
Citation: *J. Org. Chem.* **1977**, *42*, 3114

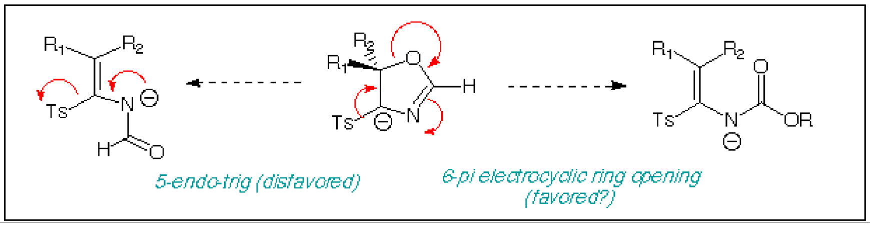
Tosylmethyl isocyanate (TosMIC) is a remarkable reagent developed by van Leusen and co-lworkers at the University of Groningen. One use of this reagent is for the one-carbon homologation of ketones to nitriles as illustrated below (*J. Org. Chem.* **1977**, *19*, 3114). In the illustrated application, Roush has applied this methodolgy to his synthesis of dendrobine (*J. Am. Chem. Soc.* **1980**, *4*, 1390).



Provide one or more plausible mechanisms for this transformation.



**Step A commentary:** This step should probably be viewed as an electrocyclic ring opening



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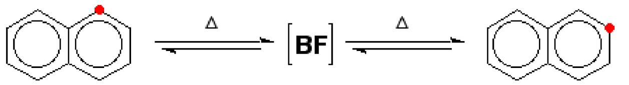
## Problem Answers

### Problem 410

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1991**, *113*, 9692

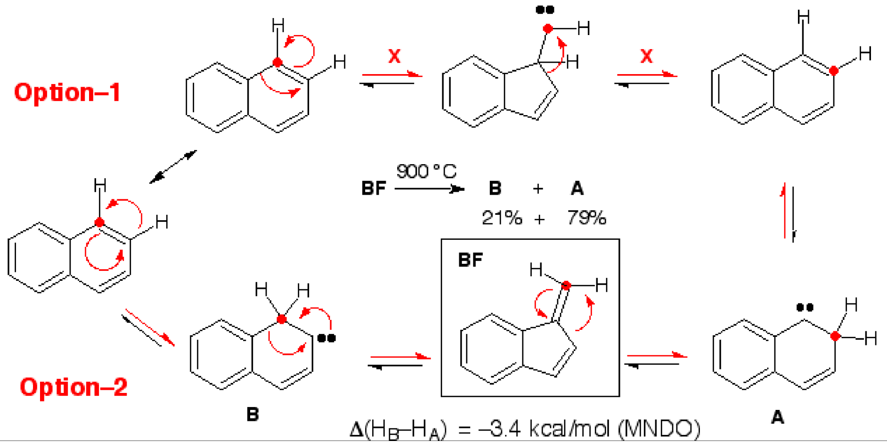
In 1977 L. T. Scott reported the remarkable automerization of naphthalene shown below (*JACS* **1977**, *99*, 4560). This study was followed up with a second report that provided aditional evidence that suggested that an intermediate, **BF**, is formed during the course of this rearrangement (*JACS* **1991**, *113*, 9692).



α–$^{13}$C-labeled $C_{10}H_8$ is isomerized into β–$^{13}$C-labeled $C_{10}H_8$ at 1035 °C

Provide one or more plausible mechanisms for this transformation and propose a reasonable structure for intermediate **BF**.

Two mechanistic proposals are provided below. Intermediate BF was synthesized and shown to partition to B and A under the reaction conditions.



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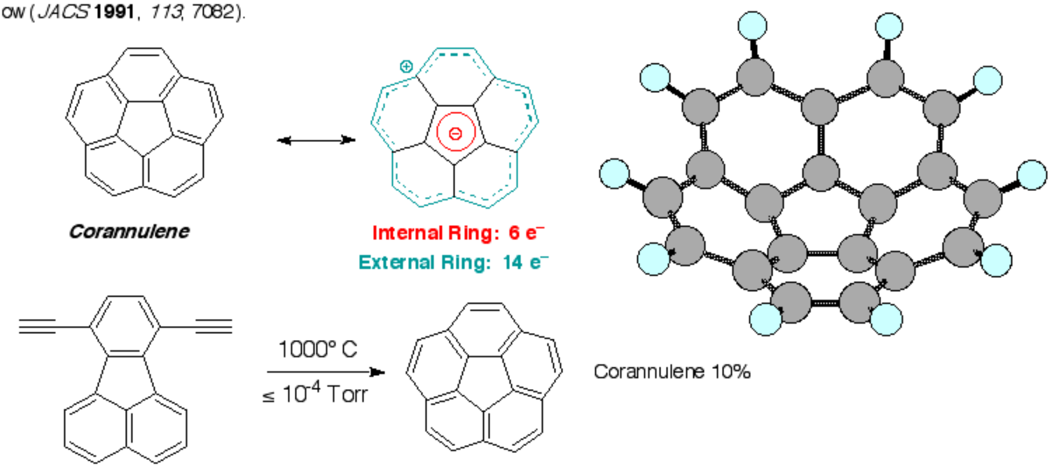
## Problem Answers

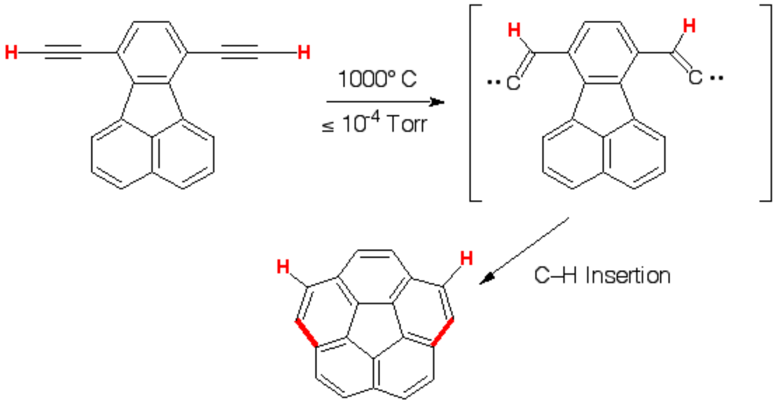
### Problem 411

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1991**, *113*, 7082

Corranulene, the bowl-shaped aromatic hydrocarbon illustrated below, is an aromatic hydrocarbon of theoretical interest. The interest in this structure follows from its polarized resonance structure that generates two internal Huckel 6– and 14–pi electron systems. the first synthesis of corranulene was reported by Lawton in 1966 through a multistep synthesis sequence (*JACS* **1966**, *88*, 380). Subsequently, L. T. Scott reported the elegant high temperature synthesis of corannulene illustrated below (*JACS* **1991**, *113*, 7082).



Provide one or more plausible mechanisms for this transformation.



This synthesis was based on the "pioneering work of R. F. C. Brown who first demonstrated the reversible rearrangement of terminal acetylenes to vinylidenes under the conditions of flash vacuum pyrolysis." LTS

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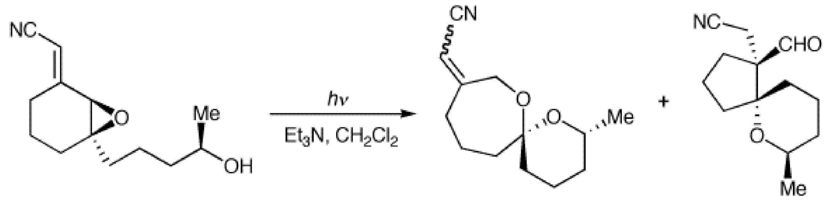
## Problem Answers

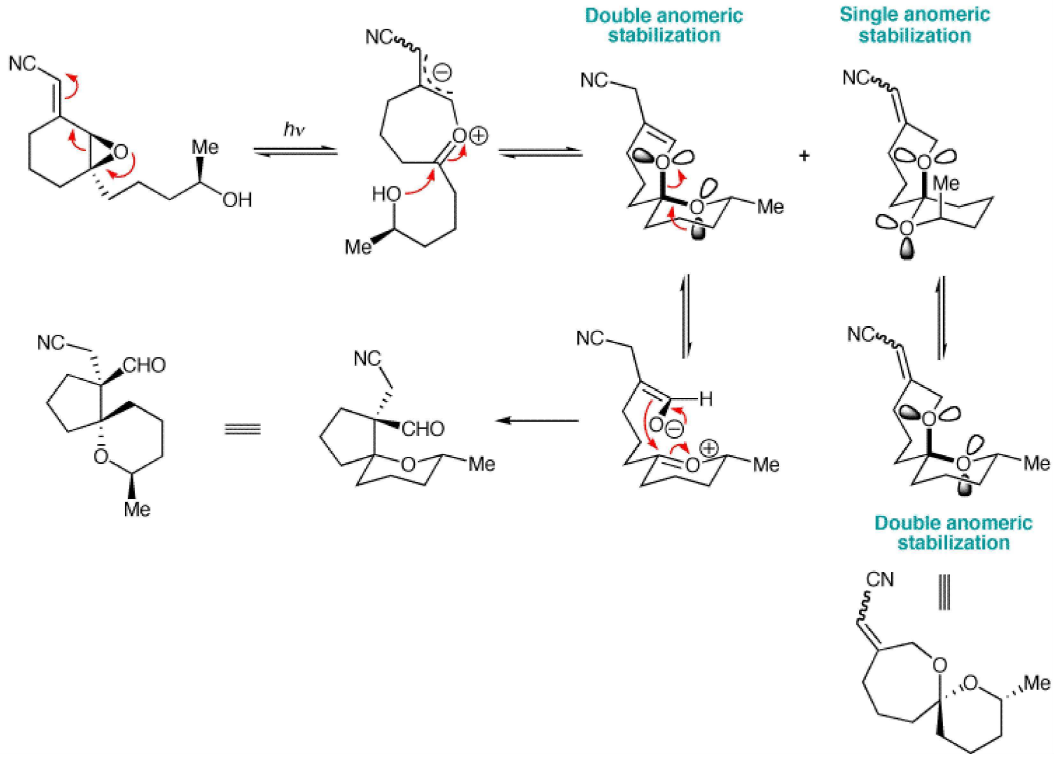
### Problem 414

Contributer: **Ryan Shenvi**
Citation: *Chem. Pharm. Bull. Japan* **1995**, *10*, 1621

Ishii and co-workers (*Chem. Pharm. Bull.* **1995**, *10*, 1621) reported photochemical reactions of several α,β–unsaturated γ,δ–epoxy nitriles, one of which is shown below.



Provide a detailed mechanism for this reaction, accounting for stereochemistry when possible.


Double anomeric stabilization
Single anomeric stabilization
NC
O
Me
OH
hν
NC
⊖
O⊕
HO
Me
NC
O
O
Me
+
NC
O
Me
O
NC
CHO
O
Me
NC
CHO
O
Me
NC
H
O⊖
⊕
O
Me
NC
O
O
Me
Double anomeric stabilization
CN
O
O
Me

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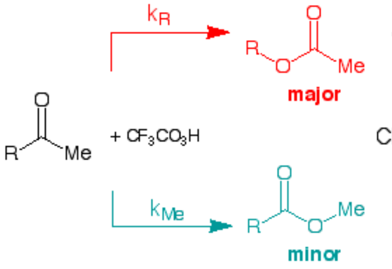
## Problem Answers

### Problem 416

Contributer: **David A. Evans**
Citation: *Angew. Chem.* **2000**, *39*, 2852

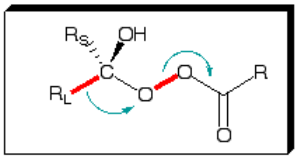
An example of a generic Baeyer-Villiger reaction is illustrated below. Precedent has established that oxygen insertion occurs preferentially between the carbonyl and the more sterically demanding C=O substituent (R). A representative set of data is provided below.



| R | $k_R / K_{Me}$ |
|---|---|
| $CH_3CH_2$ | 72 |
| $CH_3(CH_2)_2$ | 150 |
| $(CH_3)_3C$ | 830 |
| $PhCH_2$ | >2000 |

Provide a rationalization for this transformation using three-dimensional drawings. Do not ignore the important stereoelectronic issues associated with this transformation. Accordingly, begin by identifying the important HOMO-LUMO interactions.

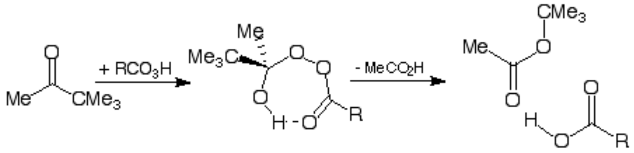
Begin by considering the illustrated Intermediate



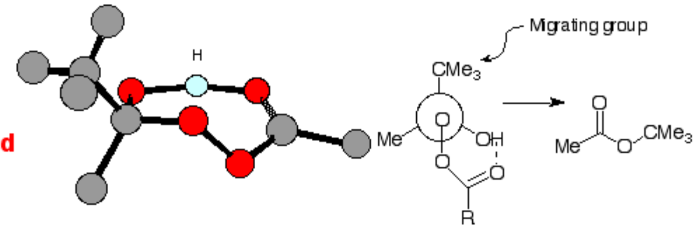
**The important stereoelectronic components to this rearrangement:**

1. The $R_L$–C–O–O dihedral angle must be 180° due to the HOMO LUMO interaction σ-$R_L$–C↔σ*–O–O.
2. The C–O–O–C' dihedral angle will be ca. 60° due to the gauche effect (O-lone pairs↔σ*–C–O).

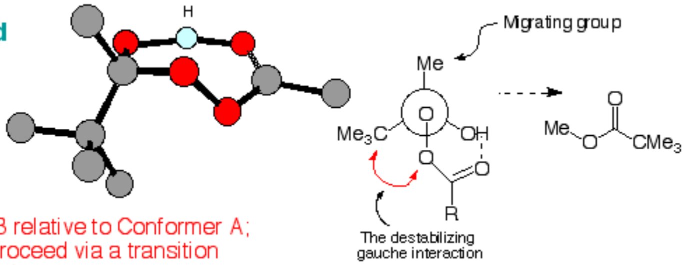
This gauche geometry is probably reinforced by intramolecular hydrogen bonding as illustrated below:



**Conformer A Favored**



**Conformer B Disfavored**



Steric effects destabilize Conformer B relative to Conformer A; hence, the reaction is thought to proceed via a transition state similar to A.

For relevant papers: Crudden, *Angew. Chem. Int. Ed* **2000**, *39*, 2852-2855 Kishi, *JACS* **1998**, *120*, 9392

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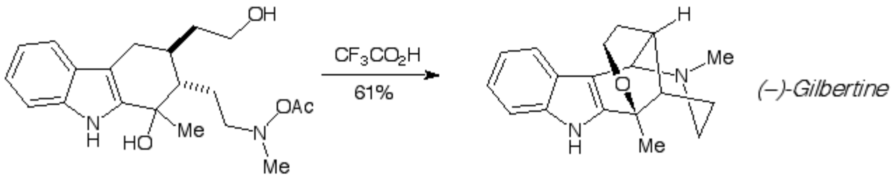
## Problem Answers

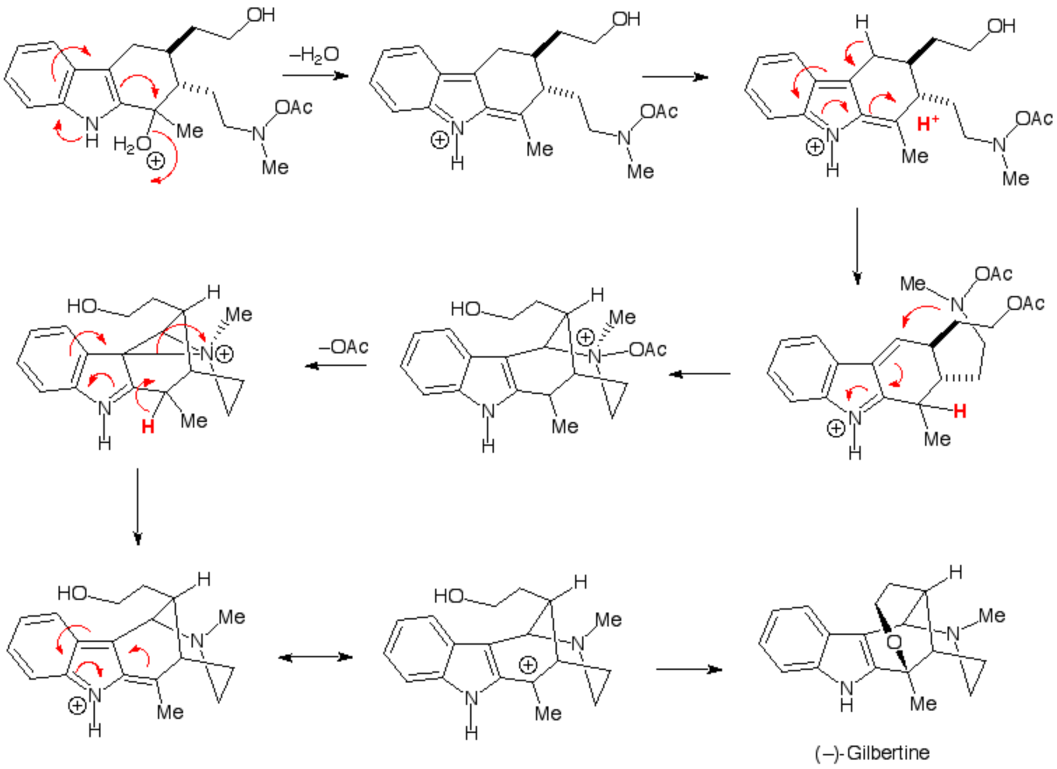
### Problem 417

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2004**, *126*, 3634-3638

An elegant synthesis of (–)-gilbertine has been recently reported by Jireck and Blechert (*JACS* **2004**, *126*, 3534-3538). The pivotal transformation in this synthesis is illustrated below:



Provide a plausible mechanism for this transformation.



This is the mechanism proposed by Blechart

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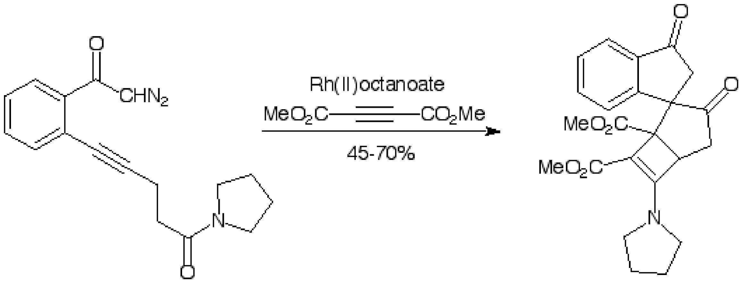
## Problem Answers

### Problem 419

Contributer: **Dan O'Malley**
Citation: *Tetrahedron Lett.* **1993**, *49*, 7853

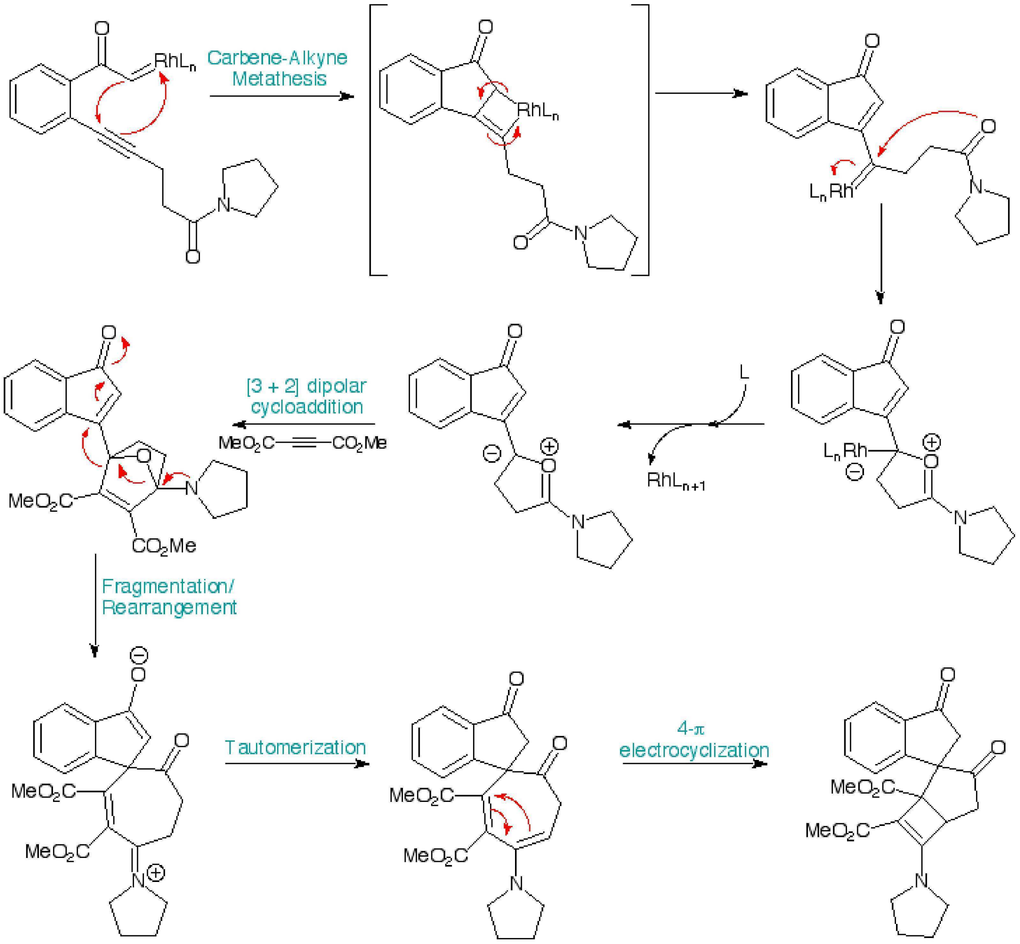
While investigating the reactivity of α-diazoketones, Padwa and co-workers (*Tetrahedron Lett.* **1993**, *49*, 7853) discovered the interesting reaction of diazoketone **1** under the conditions shown below:



**1**

**2** 1:1 mixture of diastereomers

Provide a detailed mechanism for the formation of spirocycle **2**.



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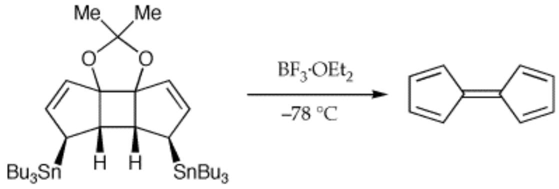
## Problem Answers

### Problem 420

Contributer: **Keith Woerpel**
Citation: *J. Org. Chem.* **2004**, *69*, 2516

In the course of their studies of unusual hydrocarbons, Myers and co-workers carried out the following transformation (*J. Org. Chem.* **2004**, *69*, 2516). Provide a mechanism.



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The answer is provided in the paper.

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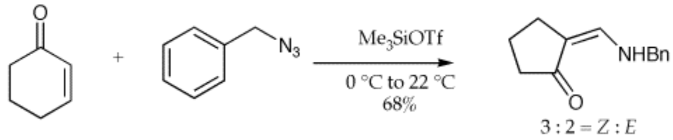
## Problem Answers

### Problem 421

Contributer: **Keith Woerpel**
Citation: *Organic Lett.* **2003**, *5*, 3899

Aubé and co-workers studied the reactions of azides with α,β-unsaturated carbonyl compounds, and they observed some interesting products (*Org. Lett.* **2003**, *5*, 3899). Provide a mechanism for the following transformation.



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The answer is provided in the paper.

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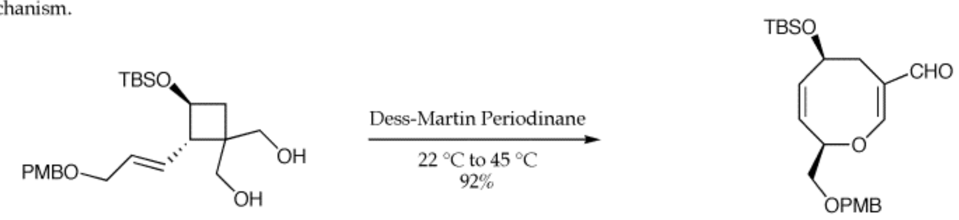
## Problem Answers

### Problem 422

Contributer: **Keith Woerpel**
Citation: *Organic Lett.* **2002**, *4*, 3891

The following transformation is a key step in Boeckman's synthesis of laurenyne (*Org. Lett.* **2002**, *4*, 3891). Provide a mechanism.



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The answer is provided in the paper.

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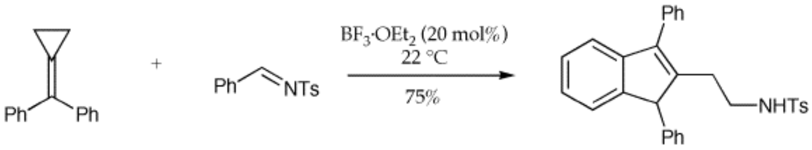
# Problem Answers

## Problem 428

Contributer: **Keith Woerpel**
Citation: *Organic Lett.* **2004**, *6*, 1175

A number of interesting transformations utilizing alkylidene cyclopropanes were recently reported (M. Shi *Org. Lett.* **2004**, *6*, 1175). Provide a mechanism for the following example.



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The mechanism is provided in the paper.

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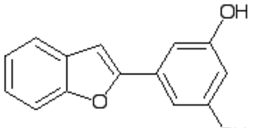
## Problem Answers

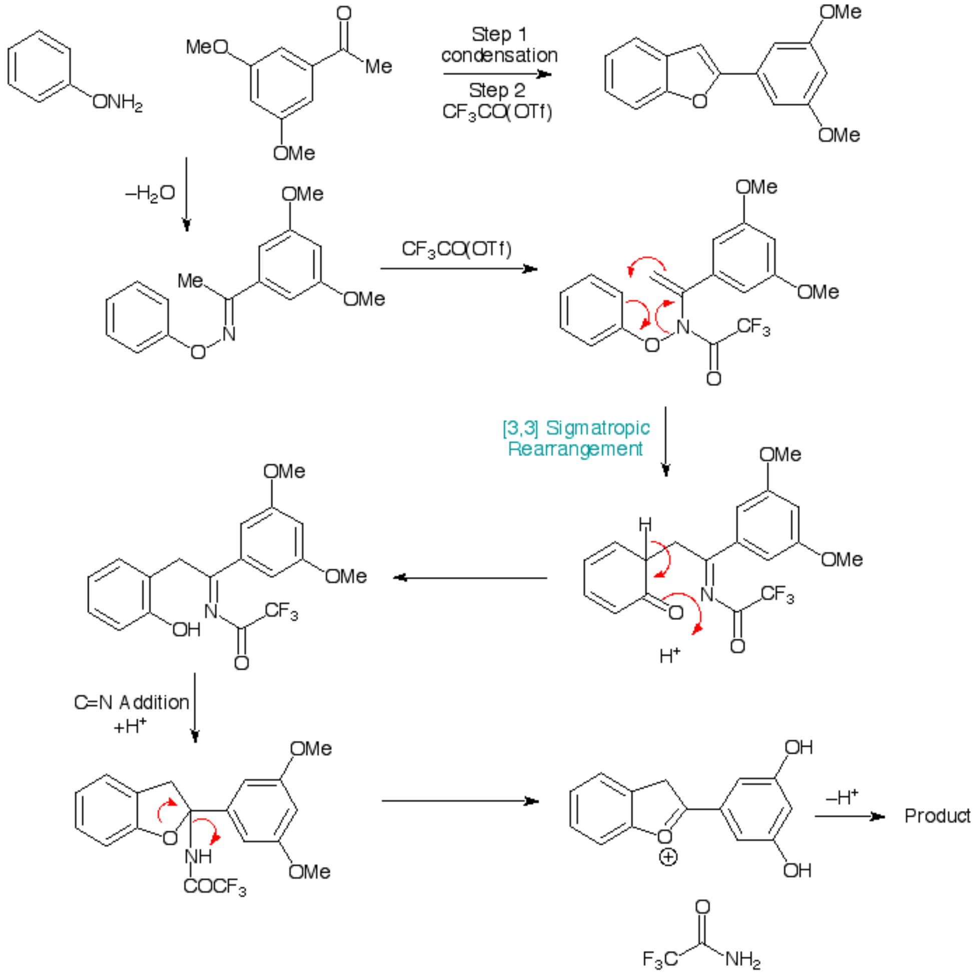
### Problem 432

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2004**, *6*, 1761

Benzofurans are widespread heterocycles in nature and are common subunits in a range of biologically active compounds. An example of a benzofuran having antifungal and insecticidal activities is stemofuran A. An approach to the synthesis of this hetercycle has recently been reported by Naito (*Org. Lett.* **2004**, *6*, 1761). The outline of the synthesis is illustrated below. The reagent employed in Step 2 is trifluoroacetyl triflate, a strong acylating agent. Provide a plausible mechanism for this transformation.



***Stemofuran A***



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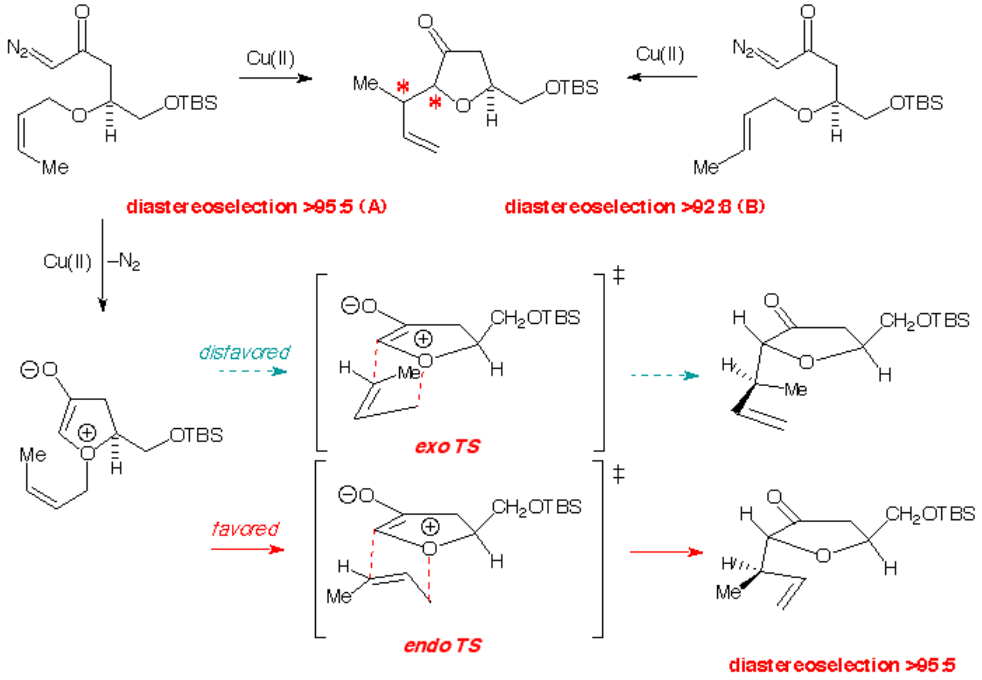
## Problem Answers

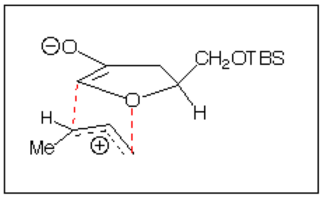
## Problem 433

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2004**, *6*, 1773

Clark and co-workers recently reported the highly stereoselective transformation of the (Z) and (E) crotyl ethers illustrated below (*Org. Lett.* **2004**, *6*, 1773–1776). As the authors note, the the literature precedents for the preferred geometry (**exo** versis **endo**) are not in universal agreement. Draw out the intermediates and transition states for the rearrangement of the (Z) crotyl ether leading to the two princpal product diastereomers. Speculate what transition state control elements might be operative to favor one of the two transition states and draw the two principal product diatereomers **A** and **B**.



The results indicate that the **endo** transition states are preferred for the rearrangements of both (Z) and (E) crotyl ethers. Since an analysis of steric effects appears to suggest that the exo TS geometry might be favored, the intervention of electronic effects could be playing a role. If the positive charge on the allyl fragment is partially delocalized, electrostatic effects might favor the ento TS geometry.



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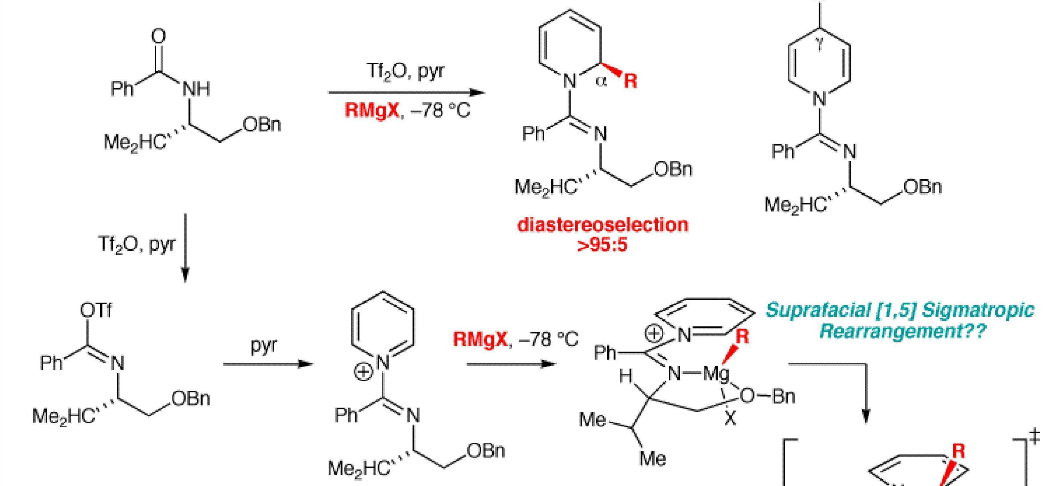
## Problem Answers

## Problem 434

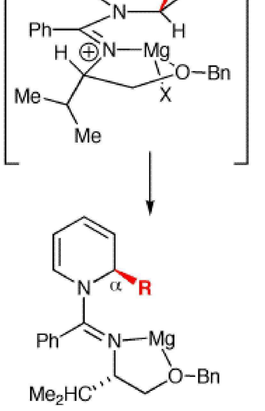
Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2001**, *123*, 11829

Charette and co-workers recently reported a creative approach to the enantioselective synthesis α-substituted piperidine derivatives illustrated below *(JACS* **2001,** *123*, 11830). The alpha regioselectivities are generally >10:1 while the alpha diastereoselections are reported to be >95:5. Provide a detailed mechanism for the overall transformation. Provide a rationalization for the stereochemical outcome of the addition reaction. Three-dimensional drawings that illustrate chirality transfer should be provided.



**diastereoselection >95:5**

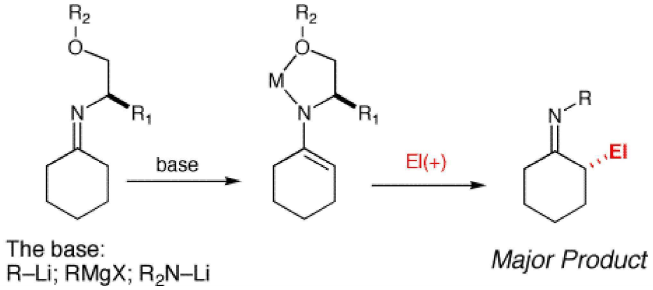
*Suprafacial [1,5] Sigmatropic Rearrangement??*



It appears that rather subtile conformational effects are operating to control selectivities between the alpha and alpha' positions. I presume that chelate organization is important to reaction diastereoselection. In this instance one might propose a suprafacial 1,5-sigmatropic rearrangement of the chelated organometal species. Steric effects might serve to orient the "R" substituent anti to the isopropyl moiety.

The use of these types of nitrogen-based chiral auxiliaries was introduced by both Meyers and Whitesell. Their applications in metalloenamine alkylation reactions is shown below.

full papers:
- Meyers, *J. Org. Chem* ***1978***, *43*, 892
- Meyers, *J. Am. Chem. Soc* ***1981***, *103*, 3081
- Meyers, *J. Am. Chem. Soc* ***1981***, *103*, 3088



The base:
R–Li; RMgX; R$_2$N–Li

*Major Product*

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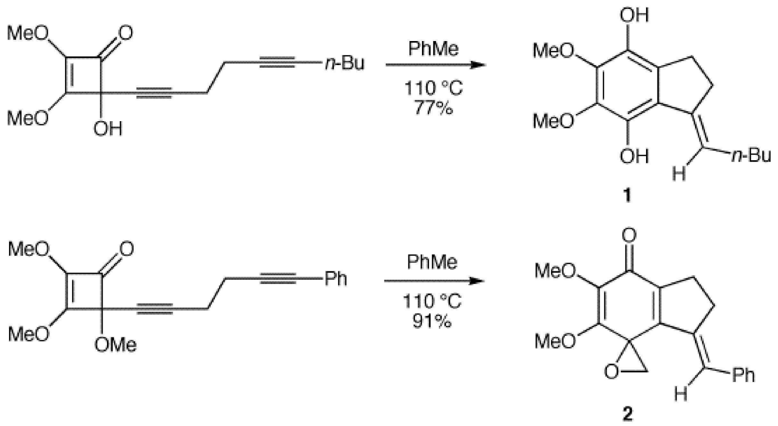
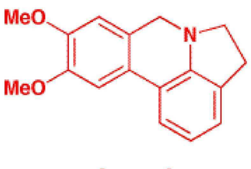
## Problem Answers

### Problem 435

Contributer: **Mihael DeMartino**
Citation: *J. Org. Chem.* **1996**, *61*, 9169

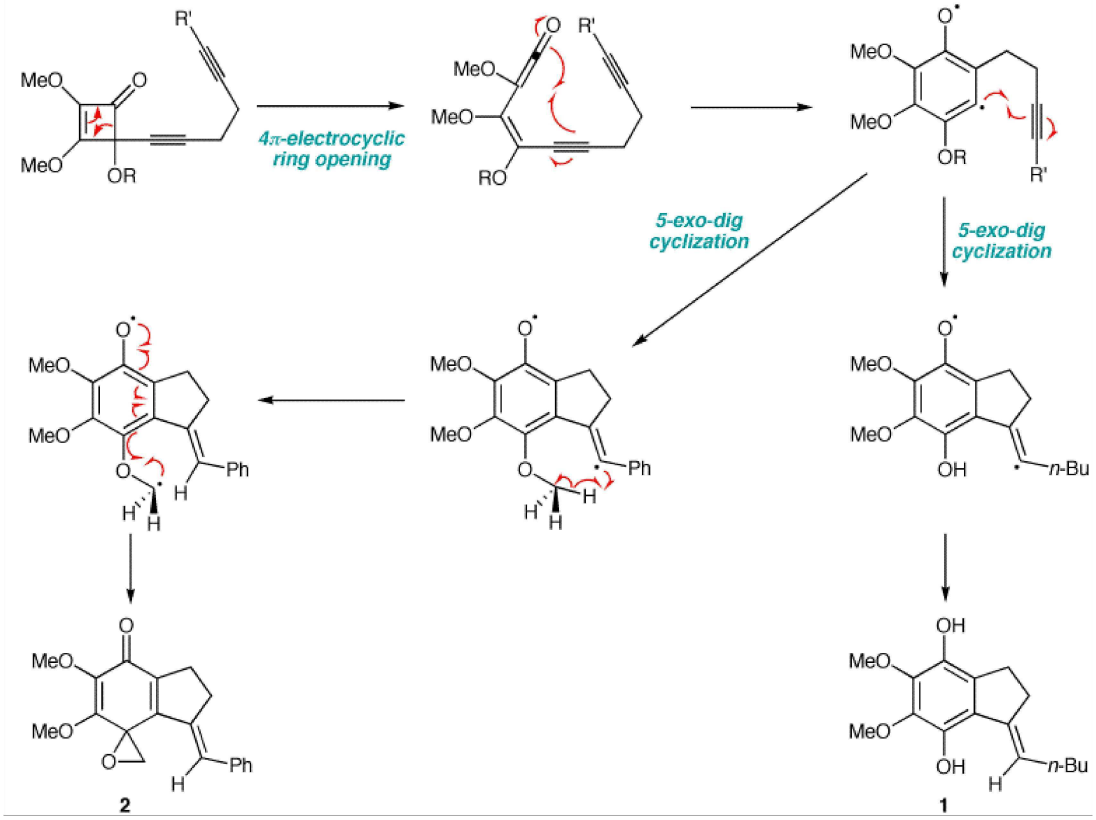
While engaged in research involving cyclobutanones, Xia and Moore discovered the following two transformations (*J. Org. Chem.* **1992**, *57*, 3765). Four years later, the first of these discoveries was employed in the total synthesis of the assoanine, **3** (*J. Org. Chem.* **1996**, *61*, 9168), a biologically interesting pyrrolophenanthride alkaloid isolated from *Amaryllidaceae* .





**Assoanine, 3**

Provide plausible mechanisms for these transformations.



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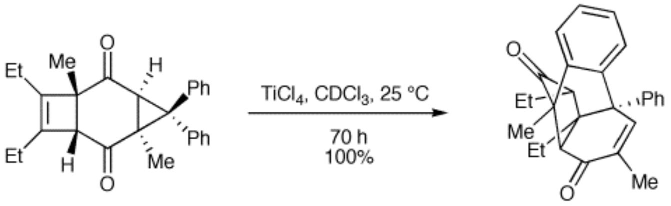
## Problem Answers

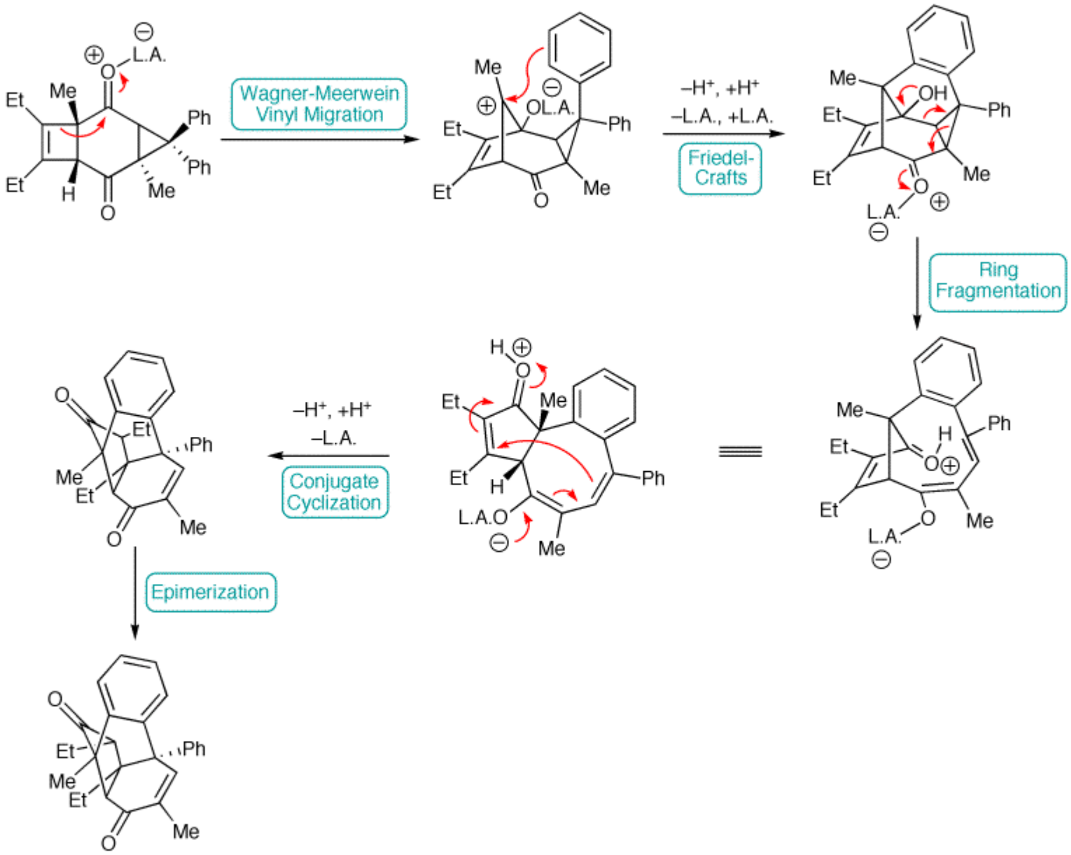
### Problem 438

Contributer: **Ryan Shenvi**
Citation: *J. Org. Chem.* **2004**, *42*, 4577

Oshima and co-workers reported the Lewis-acid catalyzed transformation of strained tricyclo[5.2.0.0]non-8-ene-2,6-diones to give, in most cases, a mixture of products (*Tetrahedron Lett.*, **2001**,*42*, 5025). In one case, however, the reaction was both quantitative and stereoselective (*J. Org. Chem.*, **2004**, *69*, 4577), yielding the quadracycle shown below.



Provide a mechanism for this transformation.



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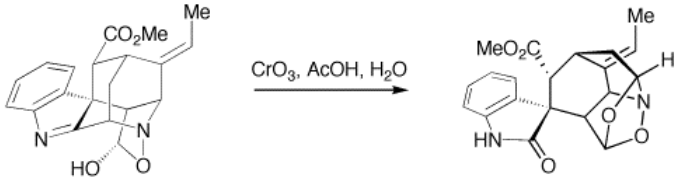
## Problem Answers

### Problem 439

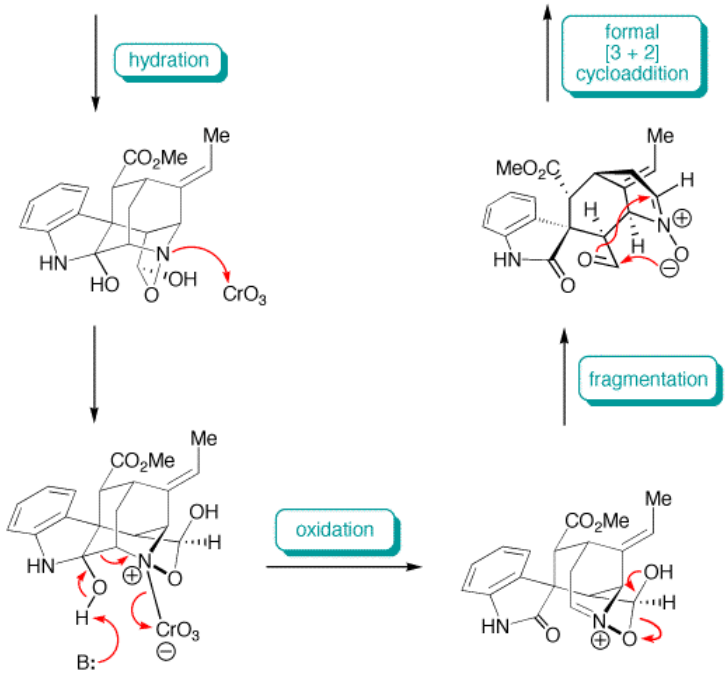
Contributer: **Carlos Guerrero**
Citation: *Helv. Chem. Acta* **1977**, *60*, 1419

While studying alkaloids isolated from *Alstonia scholaris* (Helv. Chim Acta **1977**, *60*, 1419), Schmid *et al.* discovered the hitherto-unknown indole alkaloid nareline (**1**). Oxidation ($CrO_3$, AcOH) gave structure **2**, termed "oxonareline." Provide a plausible mechanism for this conversion.



**1**: nareline **2**: oxonareline

Provide a plausible mechanism for this conversion.



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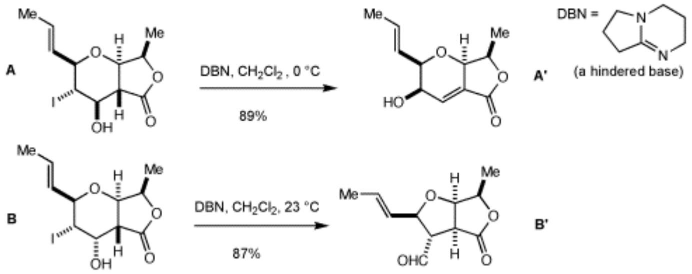
## Problem Answers

### Problem 498

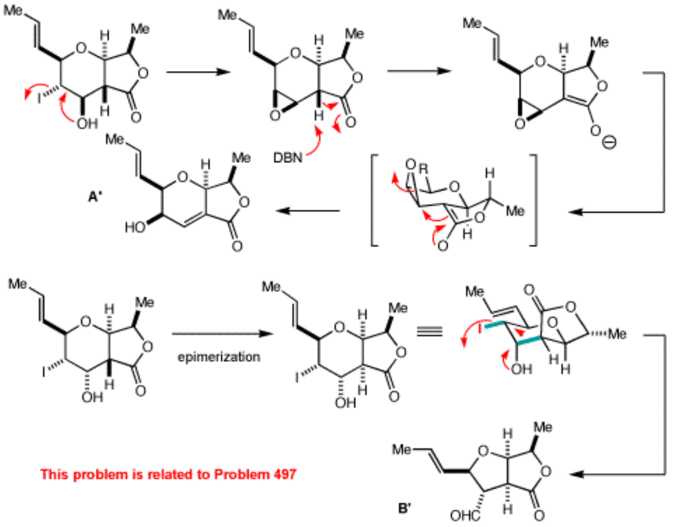
Contributer: **Pavel Nagorney**
Citation: *J. Org. Chem.* **2004**, 5517

Products from the iodoetherification (**A** and **B**), when exposed to base (DBN), undergo different rearrangements. Please provide mechanisms that account for the divergent reaction pathways.



Your Answer

Snider, *JOC*, **2004**, 5517.
Snider, *Org. Lett.* **2003**, 451-454



This problem is related to Problem 497

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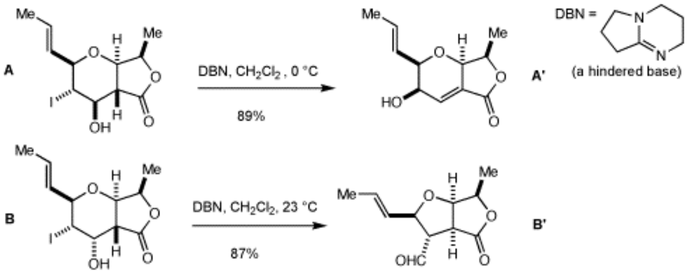
## Problem Answers

### Problem 499

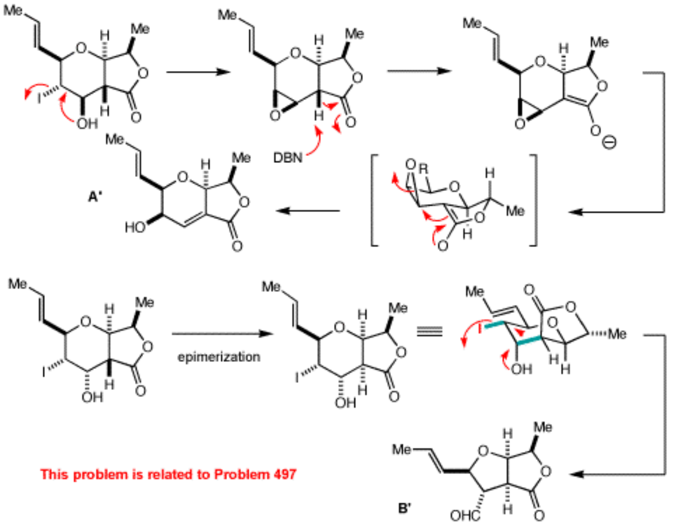
Contributer: **Jon Scheerer**
Citation: *J. Org. Chem.* **2004**, 5517

Products from the iodoetherification (**A** and **B**), when exposed to base (DBN), undergo different rearrangements. Please provide mechanisms that account for the divergent reaction pathways.



Your Answer

Snider, *JOC*, **2004**, 5517.
Snider, *Org. Lett.* **2003**, 451-454



This problem is related to Problem 497

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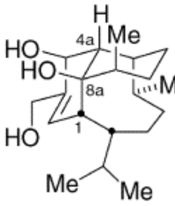
## Problem Answers

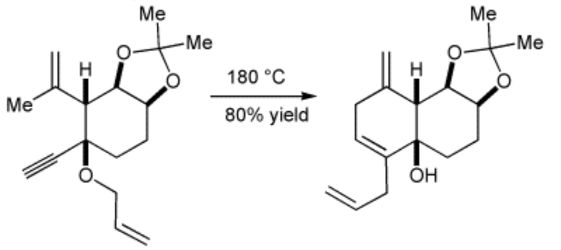
### Problem 596

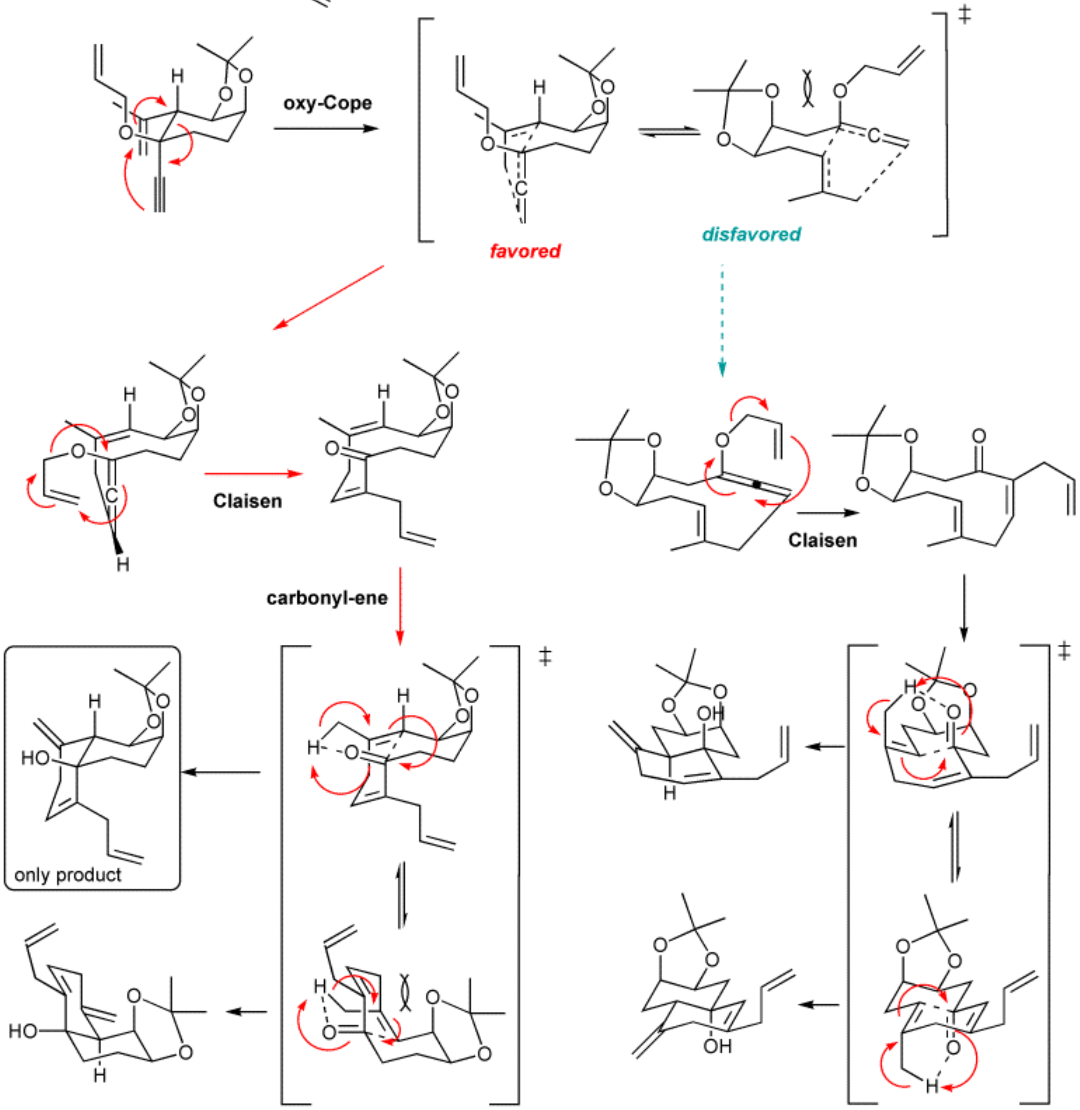
Contributer: **Louis Morency**
Citation: *Tetrahedron Lett.* **2004**, *45*, 6105

In a recent paper by Morency and Barriault (*Tet. Lett.* **2004**, *45*, 6105), the following transformation was reported. The series of thermally induced rearrangements afforded the cis decalin product as a single diastereoisomer in 80% yield. This transformation was reported as a model study for eventual application to the synthesis of vinigrol (**1**). Provide a plausible mechanism for this transformation and explain the selectivity



**1**





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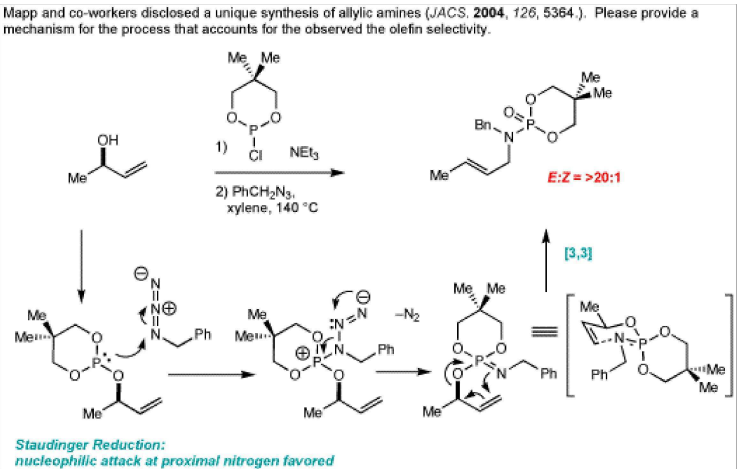
## Problem Answers

### Problem 633

Contributer: **Jon Scheerer**
Citation: *J. Am. Chem. Soc.* **2004**, *126*, 5364


Mapp and co-workers disclosed a unique synthesis of allylic amines (*JACS*. **2004**, *126*, 5364.). Please provide a mechanism for the process that accounts for the observed the olefin selectivity.

*Staudinger Reduction: nucleophilic attack at proximal nitrogen favored*

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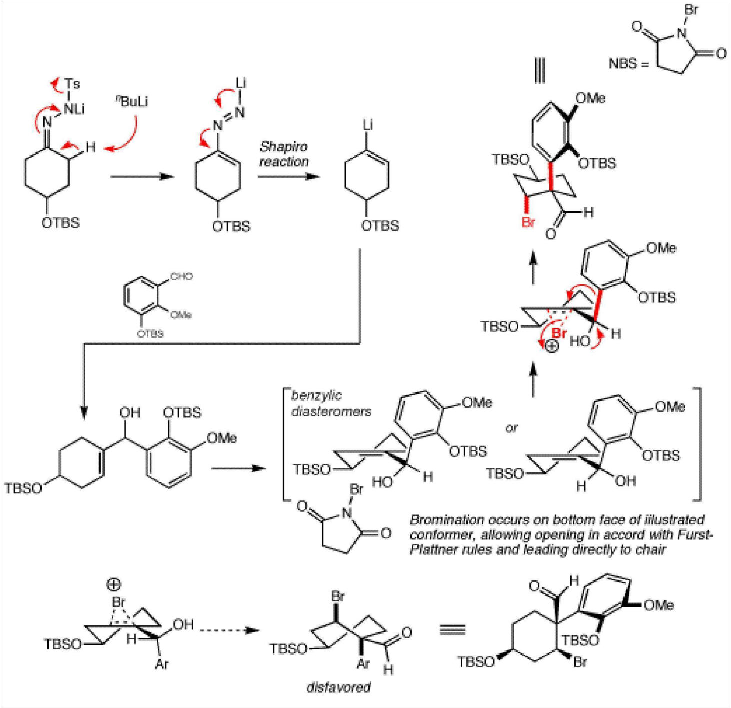
## Problem Answers

### Problem 698

Contributer: **Jon Scheerer**
Citation: *Organic Lett.* **2004**, *63*, 4691



Bromination occurs on bottom face of illustrated conformer, allowing opening in accord with Furst-Plattner rules and leading directly to chair

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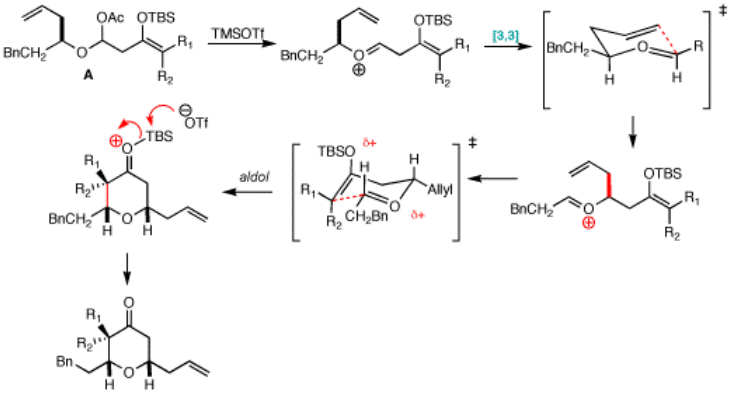
## Problem Answers

### Problem 699

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2004**, *126*, 15652



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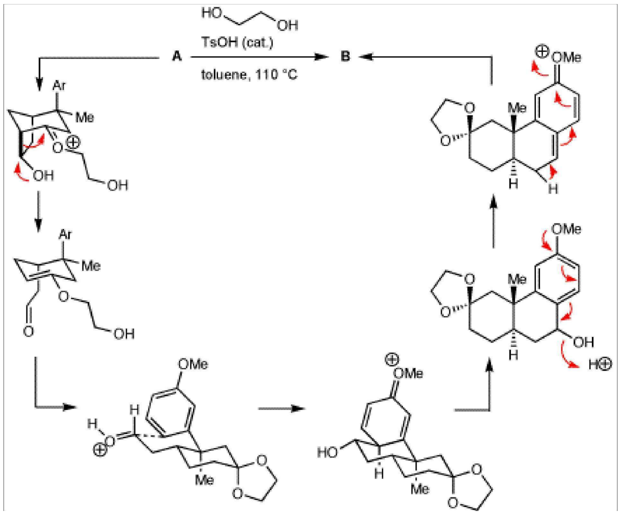
## Problem Answers

### Problem 701

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2001**, *36*, 1737



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## Problem Answers

## Problem 714

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2004**, *126*, 13600

**Scheme 2**

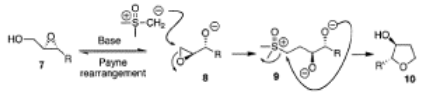
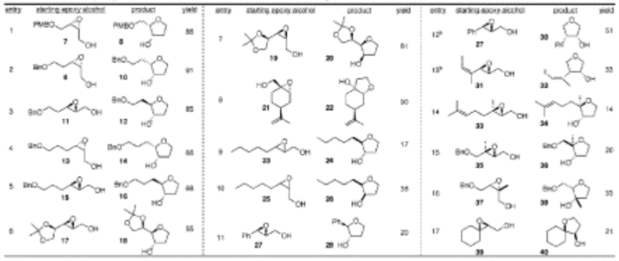


*Table 1.* Conversion of 2,3-Epoxy Alcohols to 2,3-Disubstituted THF Rings[a]



| entry | starting epoxy alcohol | product | yield |
|---|---|---|---|
| 1 | 7 | 8 | 88 |
| 2 | 9 | 10 | 91 |
| 3 | 11 | 12 | 85 |
| 4 | 13 | 14 | 88 |
| 5 | 15 | 16 | 88 |
| 6 | 17 | 18 | 55 |
| 7 | 19 | 20 | 81 |
| 8 | 21 | 22 | 90 |
| 9 | 23 | 24 | 17 |
| 10 | 25 | 26 | 38 |
| 11 | 27 | 28 | 20 |
| 12[b] | 27 | 30 | 51 |
| 13[b] | 31 | 32 | 33 |
| 14 | 33 | 34 | 14 |
| 15 | 35 | 36 | 20 |
| 16 | 37 | 38 | 33 |
| 17 | 39 | 40 | 21 |

[a] Typical reaction conditions (3.0−10.0 equiv trimethylsulfoxonium iodide, NaH, 0.1 M epoxy alcohol in DMSO, 80 °C, 36 h). [b] In THF with *n*BuLi as the base.

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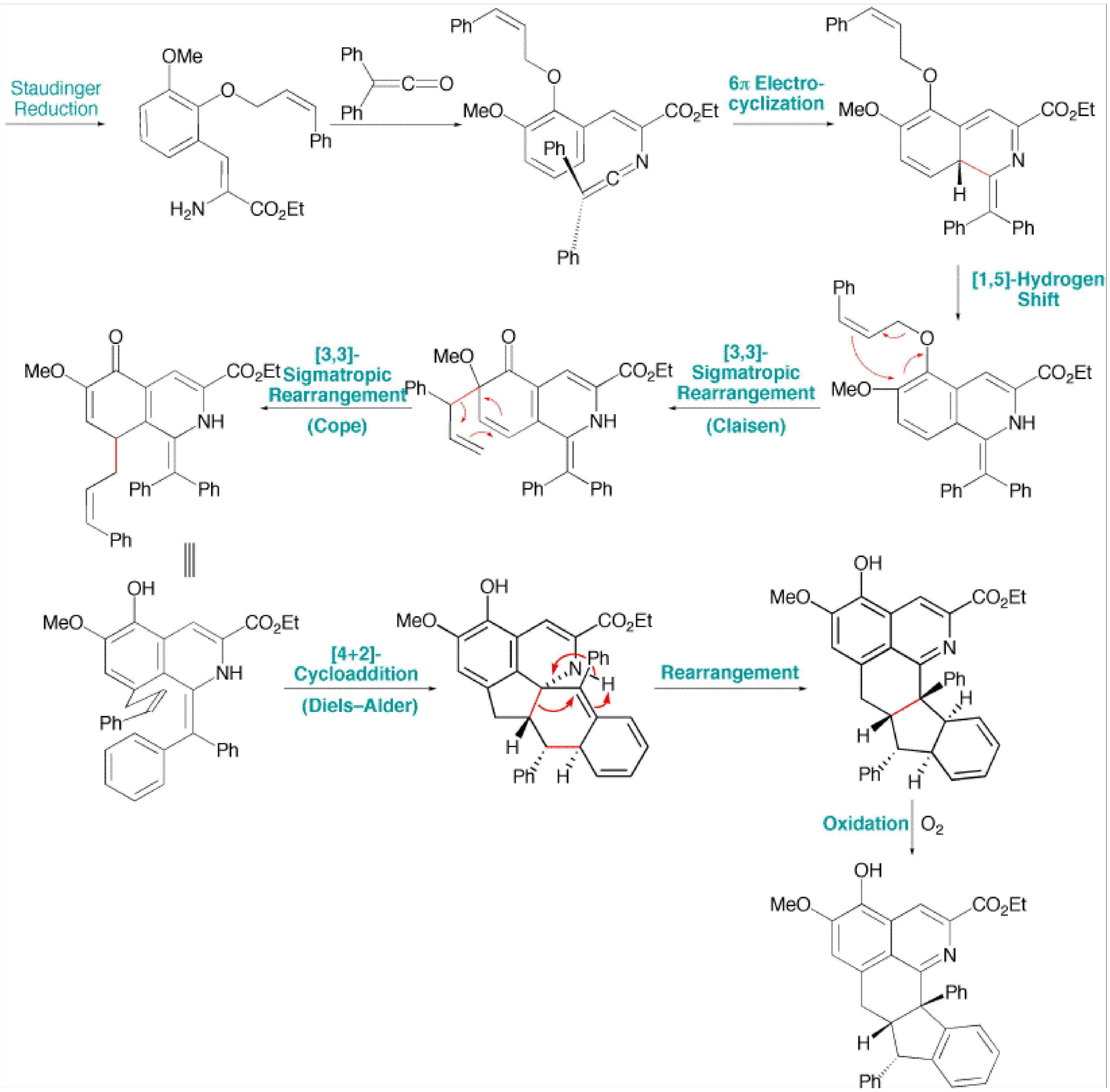
## Problem Answers

### Problem 715

Contributer: **Noah Burns**
Citation: *J. Org. Chem.* **1991**, *56*, 4006



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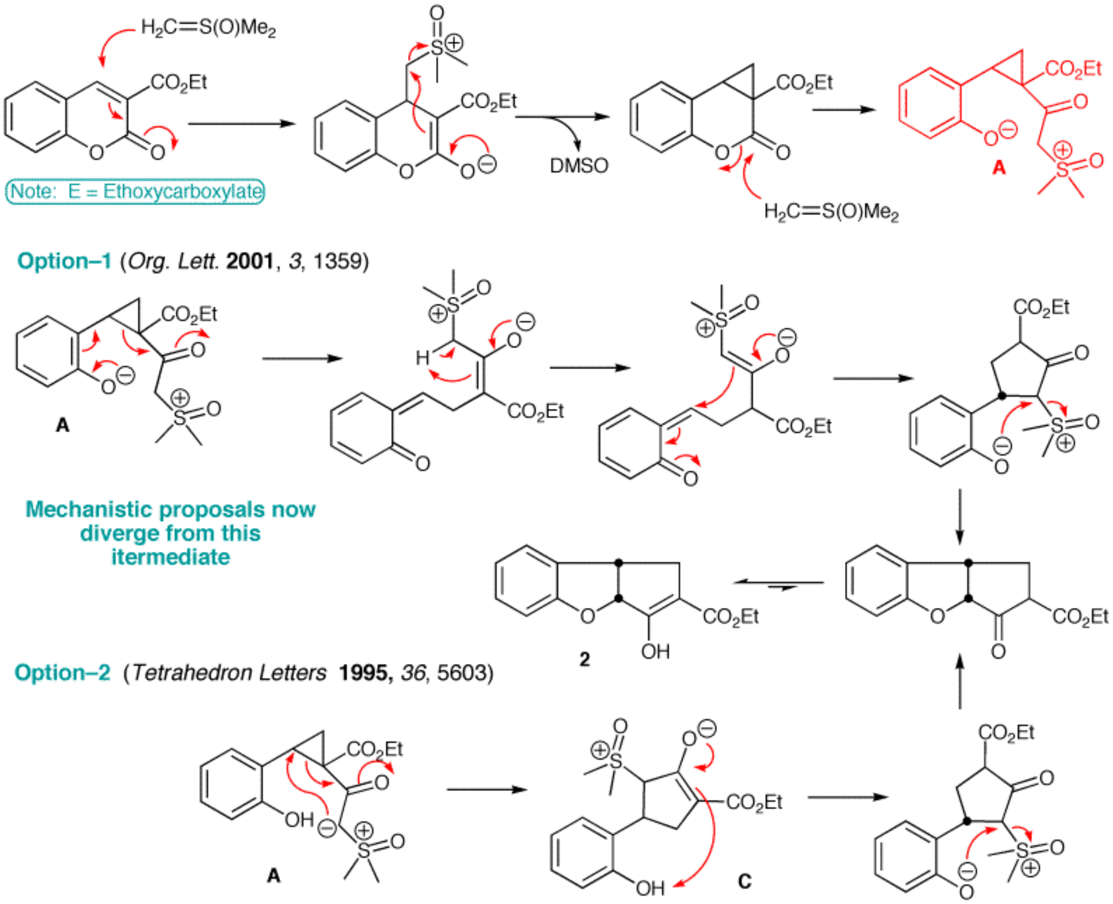
## Problem Answers

## Problem 716

Contributer: **Michael DeMartino**
Citation: *Organic Lett.* **2001**, *3*, 1359


$H_2C{=}S(O)Me_2$
$CO_2Et$
O
DMSO
A
Note: E = Ethoxycarboxylate
Option–1 (*Org. Lett.* **2001**, *3*, 1359)
Mechanistic proposals now diverge from this itermediate
2
OH
Option–2 (*Tetrahedron Letters* **1995**, *36*, 5603)
C

In the original paper, the mechanism shown in Option–2 was first proposed; however, the transformation: **A** → **C** is stereoelectronically unreasonable. In Baldwin terminology, this would be a "disallowed 4-endo-tet ring closure.

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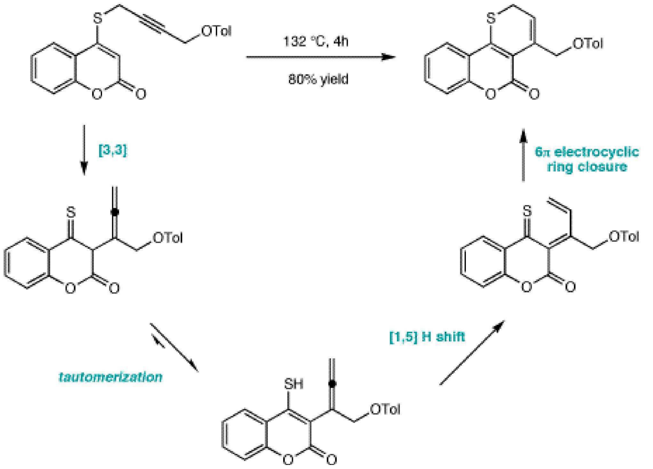
## Problem Answers

### Problem 727

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2002**, *45*, 2629

Please provide a mechanism for the following transformation (*Org. Lett.*, **2002**, 4, 2629.), being sure to classify any pericyclic processes that intervene.



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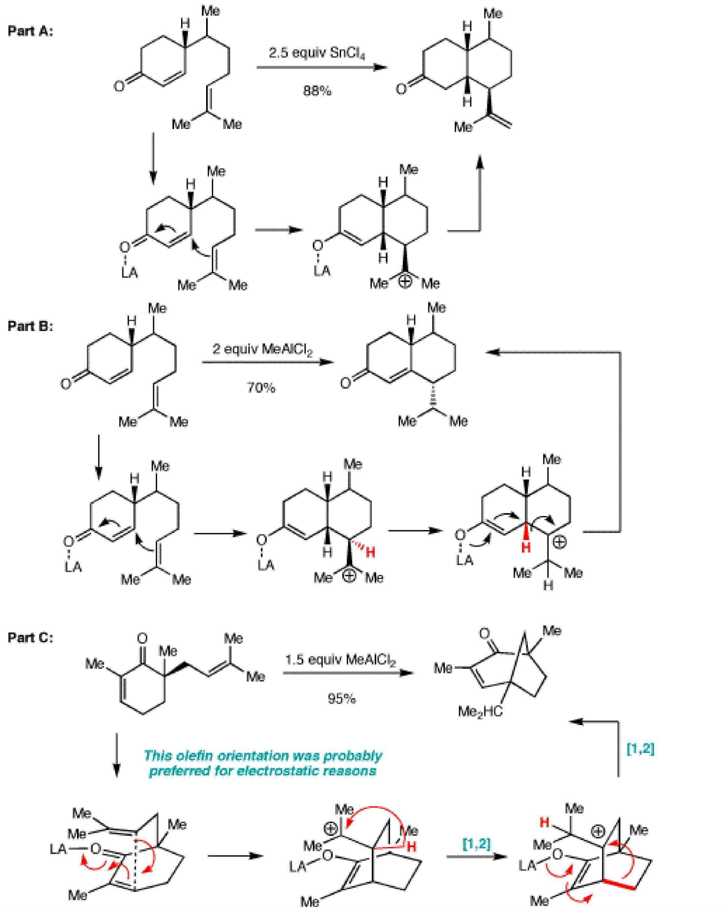
## Problem Answers

## Problem 728

Contributer: **Jon Scheerer**
Citation: *Angew. Chem.* **2005**, *44*, 9926

A recent report has investigated the cationic cyclization of olefins under Lewis acidic conditions (*ACIE*, **2005**, *44*, 99.). The following examples (**A-B**) are of increasing difficulty and are framed in a specific order. Please provide a mechanism for each case illustrated.



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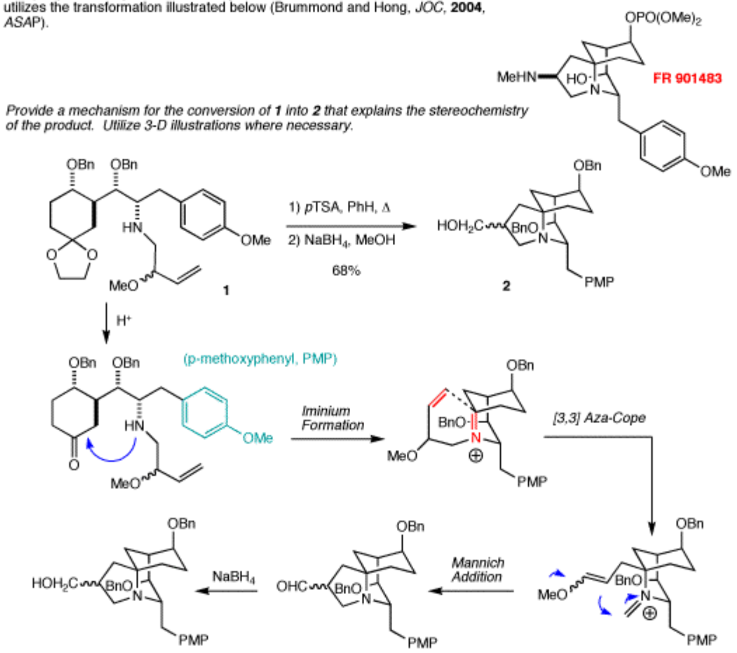
## Problem Answers

### Problem 733

Contributer: **Jon Scheerer**
Citation: *J. Org. Chem.* **2004**, *ASAP*,

FR 901483 is an immunosuppressant developed by Fujisawa Pharmaceutical Company. Recently, a formal total syntheses of FR 901483 was disclosed that utilizes the transformation illustrated below (Brummond and Hong, *JOC*, **2004**, *ASAP*).



*Provide a mechanism for the conversion of **1** into **2** that explains the stereochemistry of the product. Utilize 3-D illustrations where necessary.*

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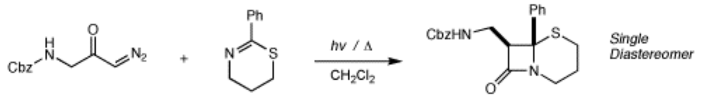
## Problem Answers

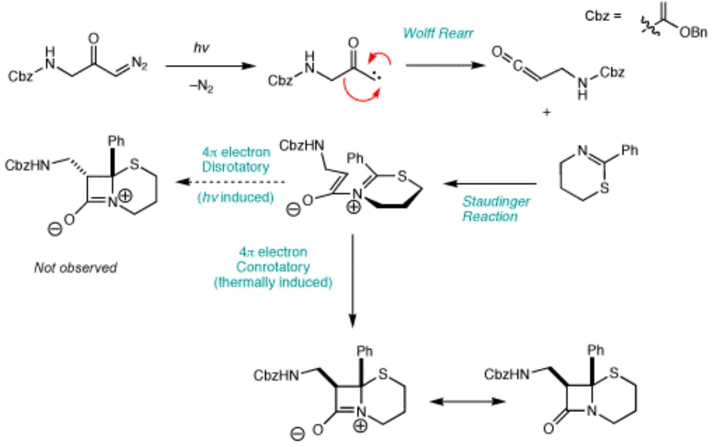
### Problem 735

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2005**, *70*, 334-337

α-Diazoketones are known to decompose to carbenes under photochemical excitation. It has recently been shown that in the presence of imines, the photo-decomposition of diazoketones provides β-lactams with good diastereocontrol (*JOC*, **2005**, *70*, 334-337).



*Provide a mechanism for the above transformation. Your answer should include an explanation for the diastereoselectivity of this process.*



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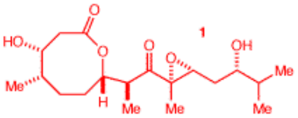
## Problem Answers

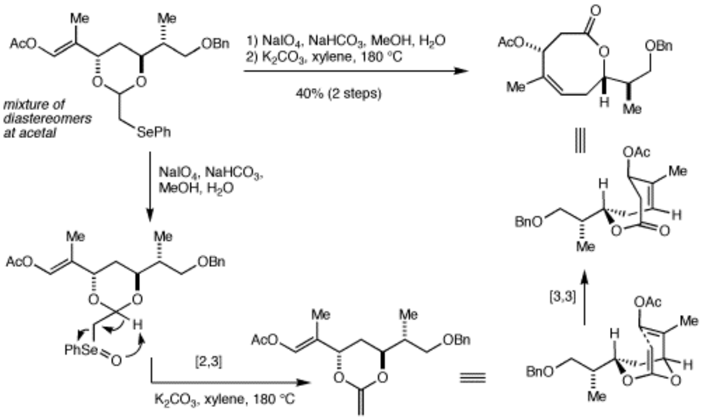
### Problem 738

Contributer: **Jon Scheerer**
Citation: *J. Am. Chem. Soc.* **2004**, *126*, 2194

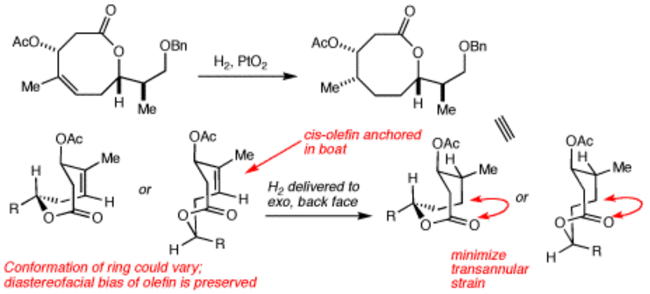
In 1991, Fenical and Clardy reported the isolation of eight-membered lactones, which were termed octalactins. The parent member, octalactin A (**1**), was recently synthesized by Holmes and co-workers (*JACS*, **2004**, *126*, 2194.).



**Part A.** Please provide a mechanism for the two-step sequence below that provides the eight-membered ring. Use 3-D illustrations in your explaination. *($NaIO_4$ is only an oxidant)*



**Part B.** Please provide a rationale for the selective hydrogenation illustrated below.


AcO
O
O
OBn
Me
H
Me
H2, PtO2
AcO
O
O
OBn
Me
H
Me
OAc
Me
H
R
H
O
O
or
OAc
Me
H
O
O
H
R
cis-olefin anchored in boat
H2 delivered to exo, back face
OAc
H
Me
H
R
O
O
or
OAc
H
Me
O
O
H
R
Conformation of ring could vary; diastereofacial bias of olefin is preserved
minimize transannular strain

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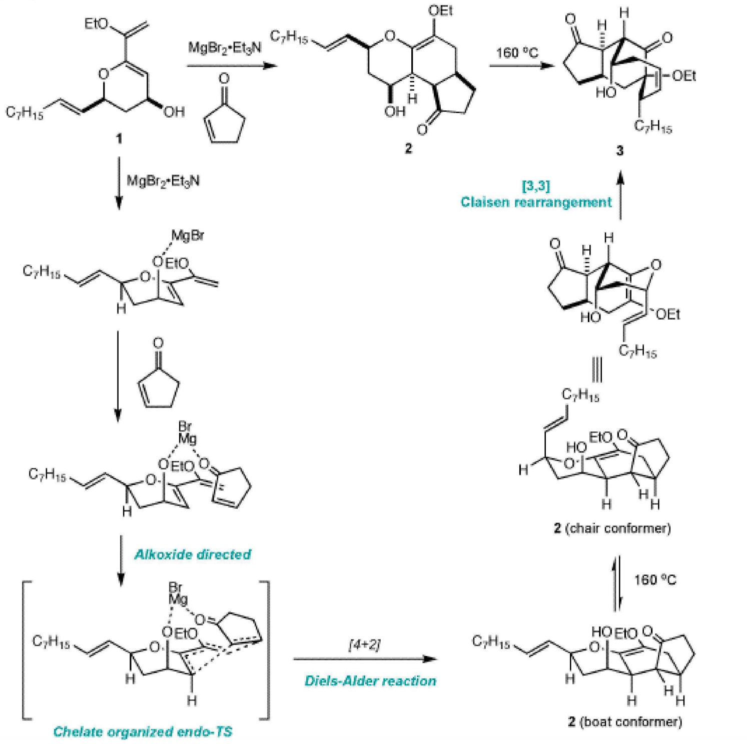
## Problem Answers

## Problem 739

Contributer: **Jon Scheerer**
Citation: *Organic Lett.* **2004**, *67*, 1317

The rapid assembly of the bicyclo[5.3.1]undecane core of penostatin F was recently reported by Barriault and coworkers (*Org. Lett.* **2004**, *6*, 1317). In this remarkable transformation dihydropyran **1** is converted to the highly complex tricycle **3** in only two operations. Please provide a detailed mechanism for this reaction sequence. Be sure to indicate all pericyclic reactions.



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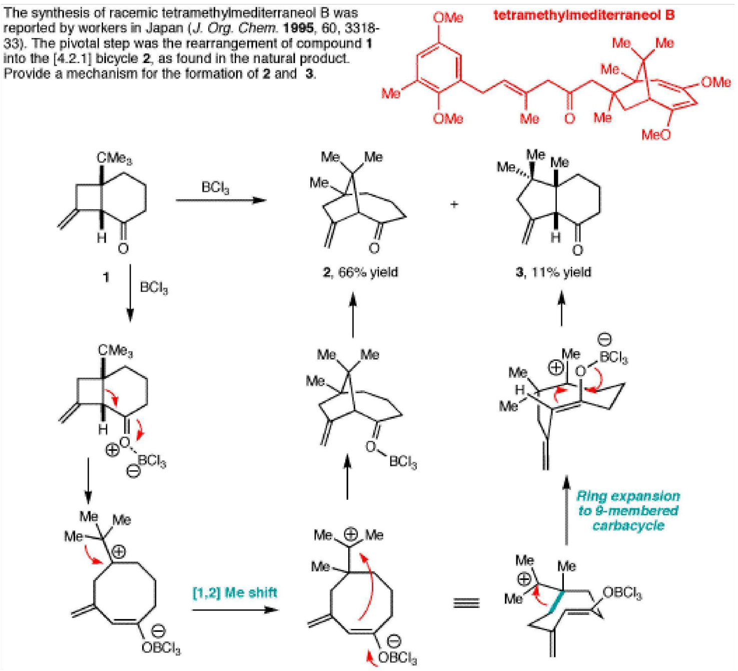
## Problem Answers

### Problem 740

Contributer: **Jon Scheerer**
Citation: *J. Org. Chem.* **1995**, *60*, 3318



The synthesis of racemic tetramethylmediterraneol B was reported by workers in Japan (*J. Org. Chem.* **1995**, 60, 3318-33). The pivotal step was the rearrangement of compound **1** into the [4.2.1] bicycle **2**, as found in the natural product. Provide a mechanism for the formation of **2** and **3**.

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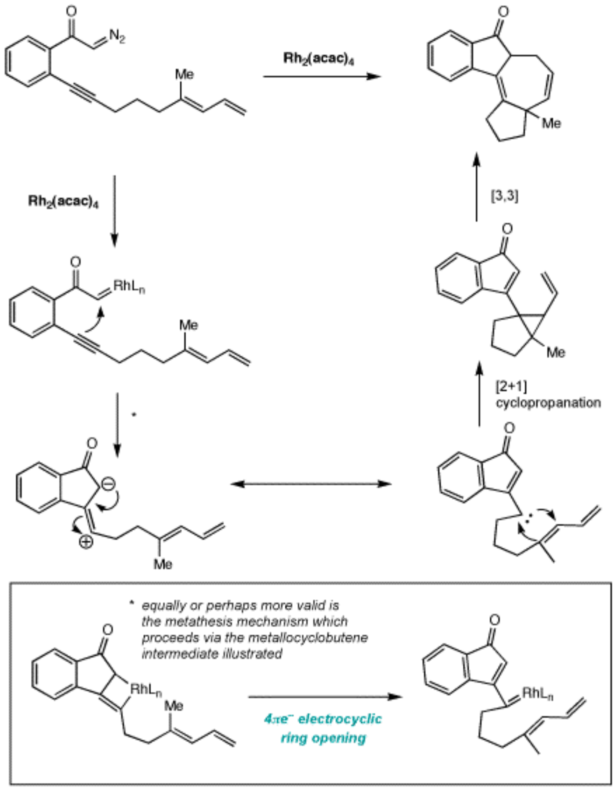
## Problem Answers

### Problem 741

Contributer: **Jon Scheerer**
Citation: *J. Org. Chem.* **1991**, *56*, 2523

Please provide a mechanism for the following transformation (*JOC*, **1991**, *56*, 2523).



* equally or perhaps more valid is the metathesis mechanism which proceeds via the metallocyclobutene intermediate illustrated

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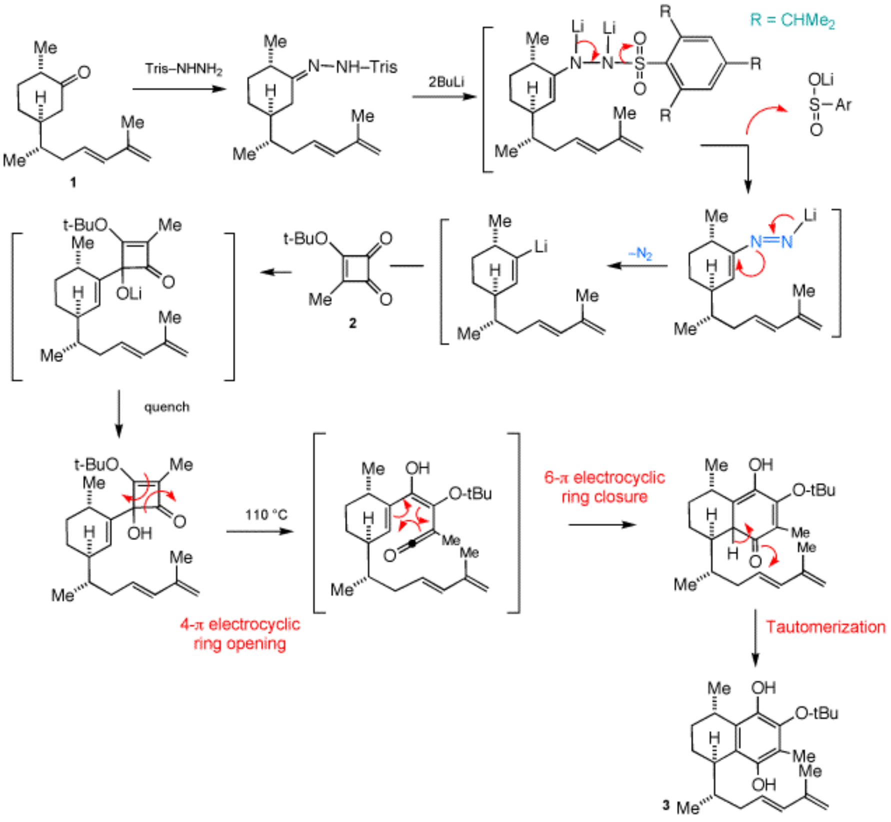
# Problem Answers

## Problem 762

Contributer: **David A. Evans**
Citation: *Angew. Chem.* **2005**, *44*, 1221-1222



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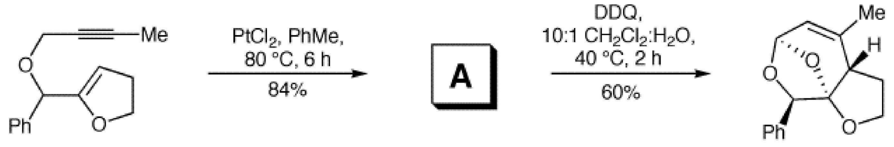
## Problem Answers

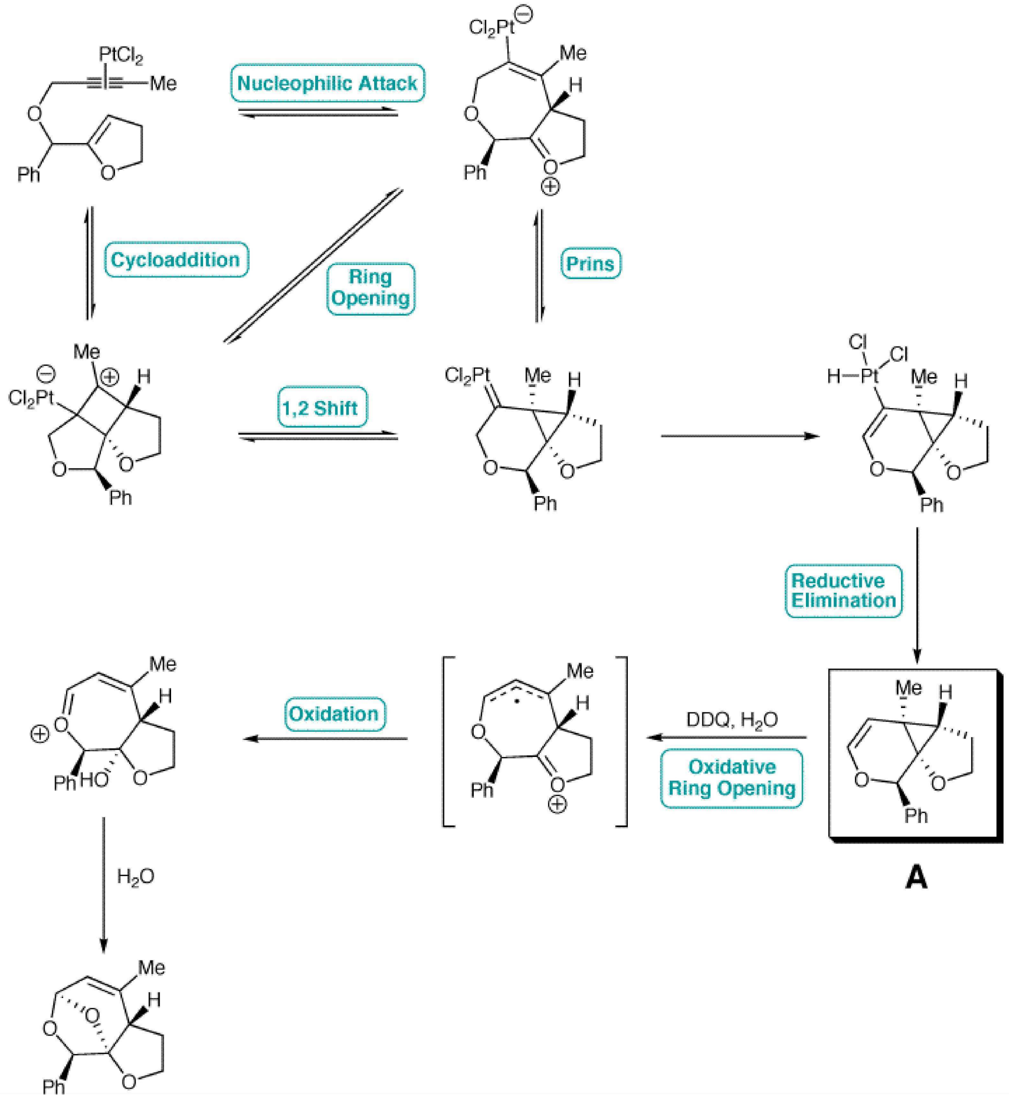
### Problem 765

Contributer: **Ryan Shenvi**
Citation: *Organic Lett.* **2004**, *6*, 3191

Based on the pioneering work of Murai (*Organometallics* **1996**, *15*, 901) and Fürstner (*J. Am. Chem. Soc.* **2000**, *122*, 6785-6786), Echavarren and co-workers (*Org. Lett.* **2004,** *6*, 3191) demonstrated the interesting sequence of transformations shown below.



Please show the correct structure of compound **A** and delineate a mechanism for each transformation.



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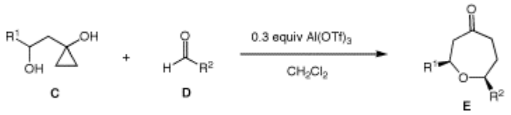
## Problem Answers

### Problem 767

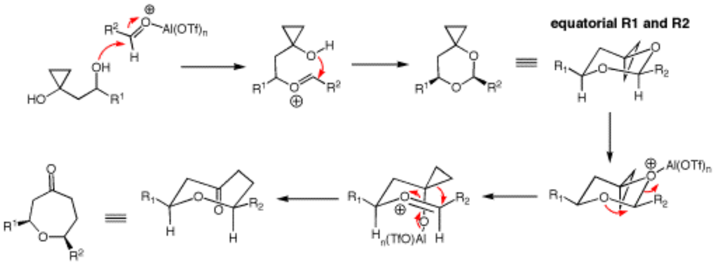
Contributer: **Karl Scheidt**
Citation: *Organic Lett.* **2005**, *7*, 515

Ring expansions can drive reactions to provide interesting products. In recent work by Minbiole and coworkers (*Org. Lett.* **2005**, *7*, 515), the combination of cyclopropane alcohol **C** and aldehydes **D** affords the seven membered rings (**E**) with catalytic quantities of Lewis acids. Provide a mechanism for this process that accounts for the observed cis-diastereoselectivity.



only cis observed
50-70% yields

Your Answer:



Minimized A(1,3) strain forces the R groups
to be both equatorial and cis
to each other.

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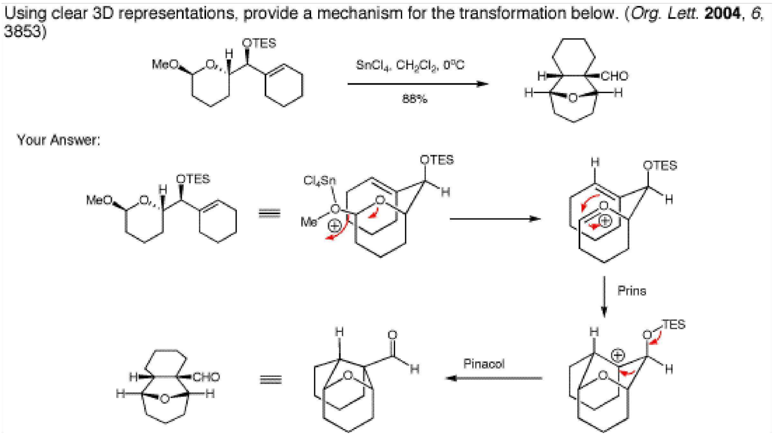
## Problem Answers

### Problem 768

Contributer: **Karl Scheidt**
Citation: *Organic Lett.* **2004**, *6*, 3853



Using clear 3D representations, provide a mechanism for the transformation below. (*Org. Lett.* **2004**, *6*, 3853)

Your Answer:

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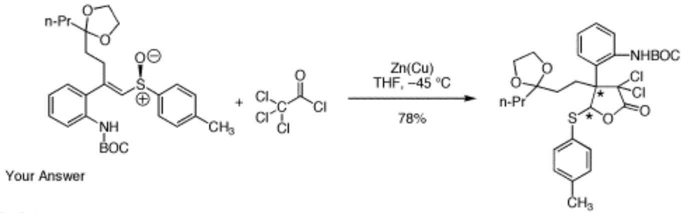
## Problem Answers

### Problem 769

Contributer: **Karl Scheidt**
Citation: *J. Am. Chem. Soc.* **2002**, *124*, 13399

In a recent synthesis of (+)-aspidospermidine by Marino (*J. Am. Chem. Soc.* **2002**, *124*, 13399), a highly diastereoselective transformation was employed utilizing sulfur to afford the γ-butyrolactone product. (shown below). Provide a detailed mechanism for this process and indicate the stereochemistry of any newly formed asymmetric centers. HINT: The Zn(Cu) reagent is a 2 electron donor that is mixed with the trichloroacetyl chloride prior to the addition of the sulfoxide.



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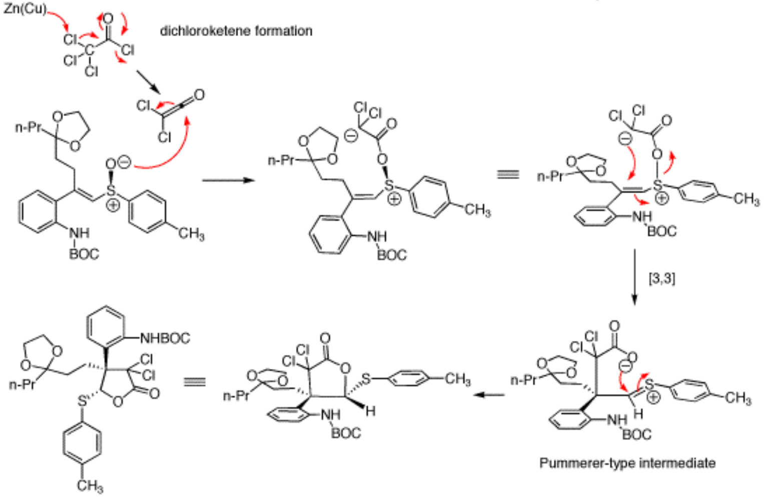

dichloroketene formation

Pummerer-type intermediate

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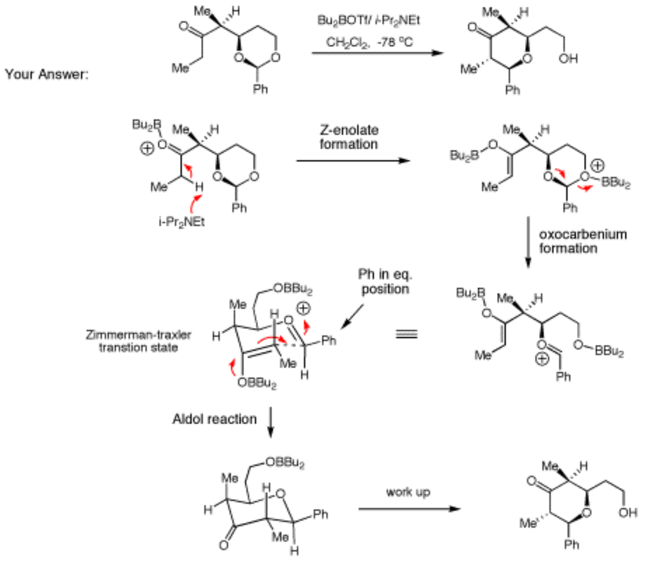
## Problem Answers

### Problem 770

Contributer: **Karl Scheidt**
Citation: *Organic Lett.* **2004**, *6*, 123

Please provide a rationale for the stereoselective synthesis of cyclic ethers in a single step shown by Sinha and coworkers (*Org. Lett.* **2004**, *6*, 123). Be sure to provide clear 3D drawing to account for the observed stereoselectivity. (Note: An excess of $Bu_2BOTf$ (> 2 equiv) is necessary for the reaction to proceed.)



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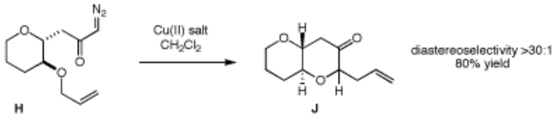
## Problem Answers

### Problem 771

Contributer: **Karl Scheidt**
Citation: *J. Am. Chem. Soc.* **2001**, *123*, 5144

The synthesis of tetrahydropyrans is an important goal in access bioactive natural products. In a dislosure by West and Marmsäter (*J. Am. Chem. Soc.* **2001**, *123*, 5144), the conversion of **H** to **J** proceeds with good yield in the presence of Cu(II) catalysts. Indicate which stereoisomer is formed and provide a mechanism for this reaction which includes a rationale for the observed diastereoselectivity.



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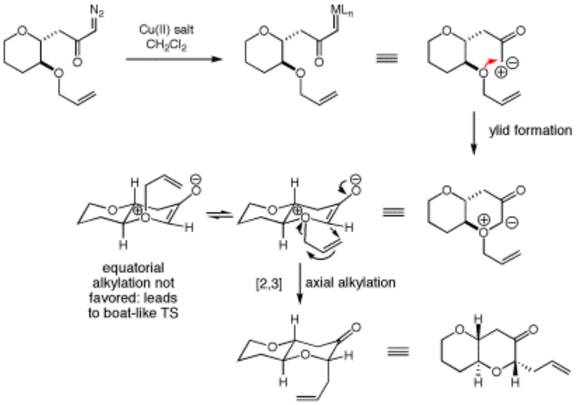

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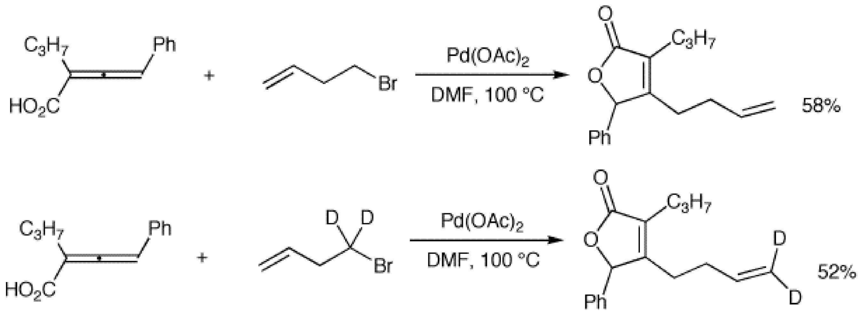
## Problem Answers

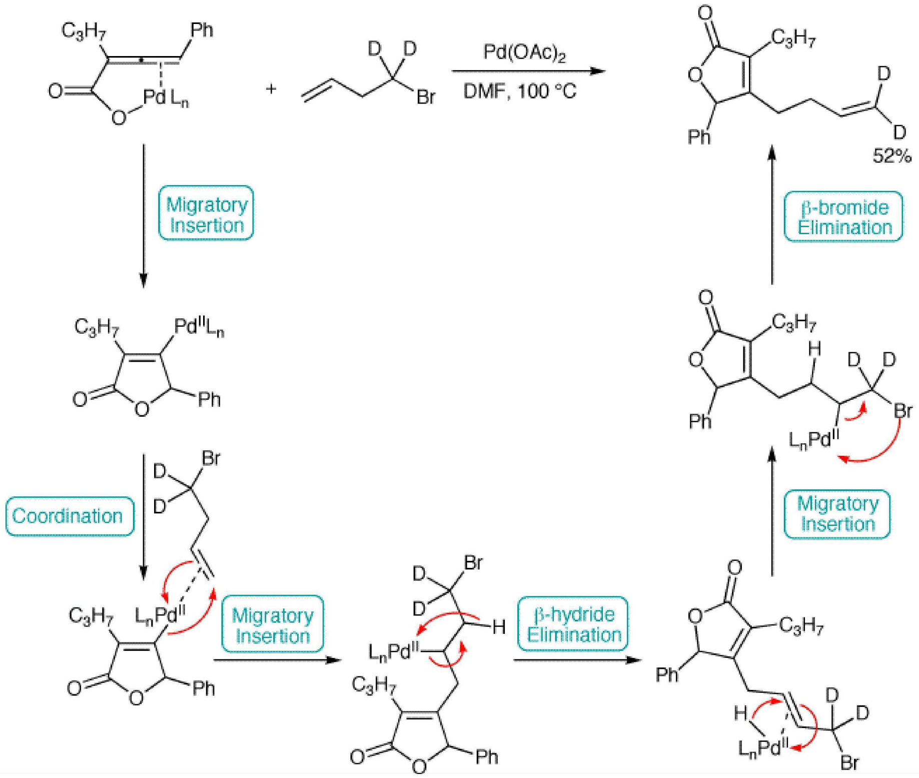
### Problem 775

Contributer: **Ryan Ashok Shenvi**
Citation: *Angew. Chem.* **2003**, *42*, 1955

In a study of the Pd-mediated coupling reaction of 2,3-allenoic acids with ω-1-alkenyl halides, compound **1** was formed as the major product in 58% yield (*Angew. Chem. Int. Ed.*, **2003**, *42*, 1955). When the deuterium labeled substrate **2** was subjected to the same reaction conditions, product **3** was obtained in 52% yield.



Propose a reasonable mechanism for the transformation that explains the fate of the deuterium atoms.



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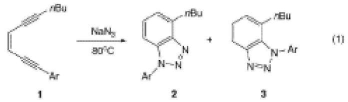
## Problem Answers

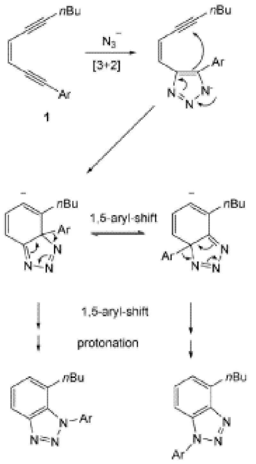
### Problem 779

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2005**, *7*, 475-477

The reaction of the illustrated ene-diyne **2** with sodium azide at 80 °C affords the benztriazoles **2** and **3**.(Org. Lett. **2005**, *7*, 475-477.



Provide plausible mechanisms for this transformation.



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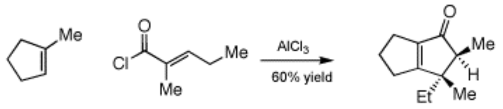
## Problem Answers

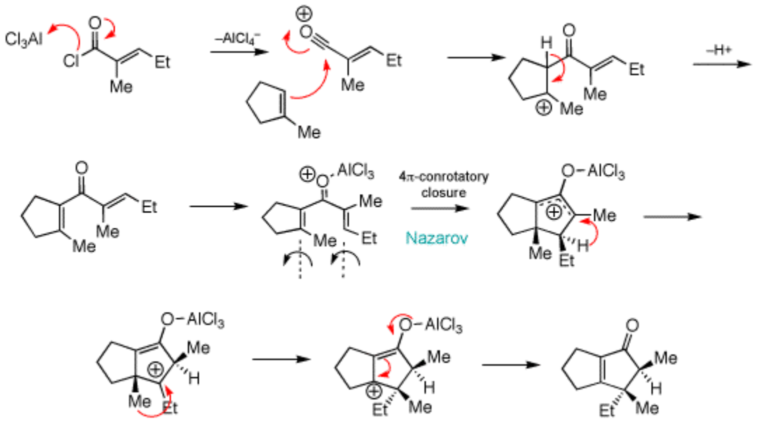
### Problem 780

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1991**, *113*, 8062-8069

Santilli and co-workers reported this Lewis acid catalyzed reaction (Santilli etal. *JACS* **1991, 113,** 8062-8069).



Please provide a reasonable mechanism for this transformation that includes the rationalization of the stereochemical outcome of the transformation.



For a recent review of the Nazarov reaction see: M. A. Tius, European J. Chem. 2005, 2193

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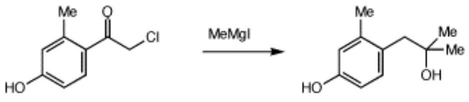
## Problem Answers

### Problem 782

Contributer: **Ian Fleming**
Citation: *Tetrahedron Lett.* **1972**, 895

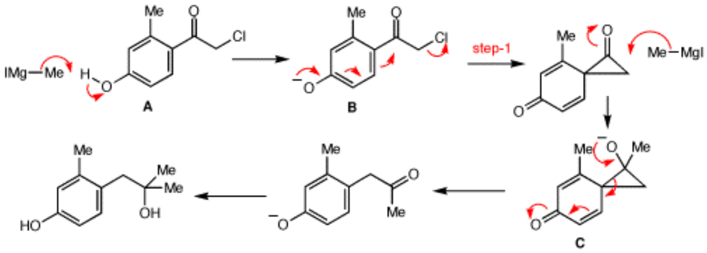
Bohlmann and Kapteyn treated the ketone with MeMgI and obtained an unexpected product (*Tetrahedron Lett.*, **1972**, 1895.).



Account for the formation of this product.

The α-chloroketone is susceptible to a Favorskii-like step **B**, because the removal of the proton from the phenolic oxygen **A** is easy, setting up an extended enolate. The opening of the cyclopropanone **C** is also easy and highly (a) chemo- and (b) regioselective. (a) The cyclopropanone carbonyl is more electrophilic than the other carbonyl group, because it is exocyclic to a strained ring, and not conjugated. (b) Although cyclopropanones in Favorskii reactions usually open to the less-substituted side, the charge on the more-substituted side in this case is largely taken up on the phenolic oxygen, and simultaneously the aromatic ring is restored.

It is possible, but unlikely, that the Grignard attacks the ketone *before* cyclopropanone formation, but the removal of the proton from the phenolic oxygen is likely to be fast, and conjugation between the phenolate and the ketone carbonyl would make the carbonyl group less electrophilic.



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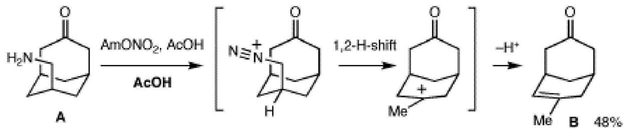
# Problem Answers

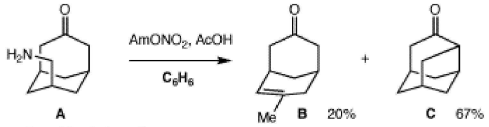
## Problem 784

Contributer: **Ian Fleming**
Citation: *J. Org. Chem.* **1973**, *38*, 3462

Primary amines on treatment with nitrous acid give diazonium ions. These reactive intermediates are only isolated when the amine is aromatic. With aliphatic amines, the diazonium ion is a reactive intermediate which usually undergoes elimination or substitution reactions, sometimes preceded by cationic rearrangement. This was the result with the primary amine **A** when the reaction was carried out in acidic solution: the unsaturated ketone **B** was the major product (J.-H. Liu and P. Kovacic, *J. Org. Chem.*, 1973, **38**, 3462).

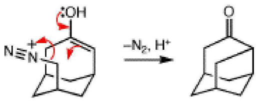


However, Liu and Kovacic found that, when the amount of acid was limited to one molar equivalent, the major product was the saturated ketone **C**.



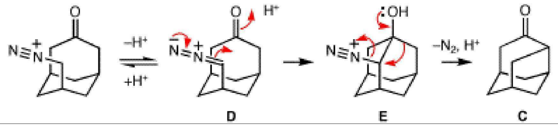
Account for the formation of the ketone **C**.

The "obvious" mechanism is for the enol of the ketone to attack the diazonium ion:



but there are good reasons to doubt this:
(a) Diazonium ions are reactive, and rarely have a lifetime long enough to give the ketone time to enolise. This is an illustration of a general observation, that intermediates are rarely doubly activated.
(b) It does not explain why the reaction is seen only with a limited amount of acid, when acid can be expected to catalyze the formation of the enol.

It is more likely that the diazonium ion is in equilibrium with the diazoalkane **D**, which will be formed in higher concentration when the amount of acid is limited. The diazoalkane can nucleophilically attack the ketone group, and the intermediate **E** undergo a 1,2-alkyl shift to give the product. The reaction of diazoalkanes with ketones giving insertion like this is well known; cyclohexanone and diazomethane give cycloheptanone for example.



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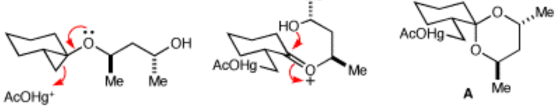
## Problem Answers

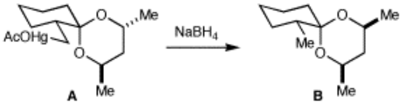
### Problem 785

Contributer: **Ian Fleming**
Citation: *Tetrahedron Lett.* **1993**, *34*, 505

Mercuric ions are soft electrophiles, which attack alkenes and even cyclopropanes, as in the reaction forming the organomercury intermediate **A**:

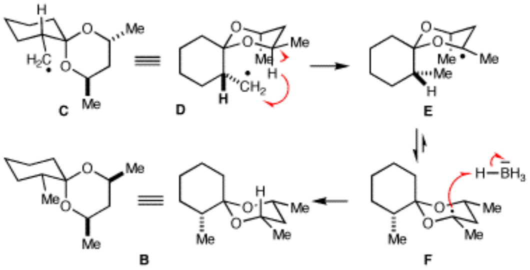


Normally the mercury is removed by reduction with sodium borohydride in a radical chain reaction. In the case of the mercury derivative A, however, Sugimura found that an unexpected change in configuration in the 1,3-dioxan ring took place when this reaction was carried out on the mercury compound **A**, giving the product **B** (T. Sugimura, S. Goto, K. Koguro, T. Futagawa, S. Misaki, Y. Morimoto, N. Yasuwaka and A. Tai, *Tetrahedron Lett.*, **1993**, *34*, 505).



Explain this result.

The borohydride creates a mercury hydride, which is very susceptible to the formation of a mercury radical. The mercury radical then loses $Hg^0$, to create the primary radical **C**. Normally this would rapidly abstract a hydrogen atom from a borohydride ion, to give a methyl group and a boron radical which can continue the chain reaction. In this case, however, the primary radical has a hydrogen atom held quite close to it **D**, and a 1,5-hydrogen atom transfer gives the considerably more stabilized radical **E**. After a change to the more stable conformation **F**, in which all the substituents are equatorial, this now reacts with a borohydride ion, with the hydrogen atom approaching for stereoelectronic reasons from the axial direction.



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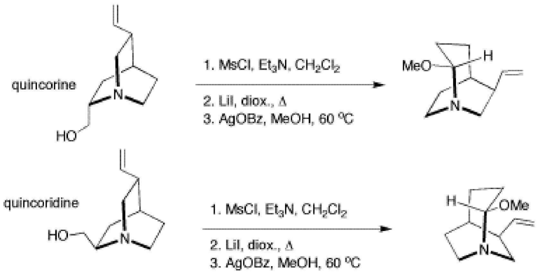
## Problem Answers

## Problem 786

Contributer: **Robert M. Williams**
Citation: *Organic Lett.* **2000**, *2*, 1661

Hoffman, et al., reported the interesting ring expansion reaction of azabicyclo[2.2.2]octanes as shown below. Please provide a mechanistic rationalization for this transformation. Note that complete stereospecificity is observed from the two diastereomers quincorine and quincoridine; your mechanism should account for the observed stereospecificity.
(Roper, S.; Frackenpohl, J.; Schrake, O.; Wartchow, R.; Hoffmann, M.R., *Org. Lett.* **2000**, *2*, 1661; Roper, S.; Wartchow, R.; Hoffmann, M.R., *Org. Lett.* **2002**, *4*, 3179)



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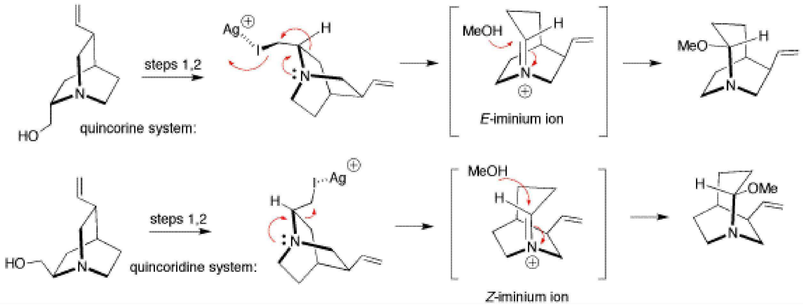

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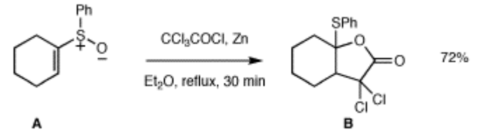
# Problem Answers

## Problem 787

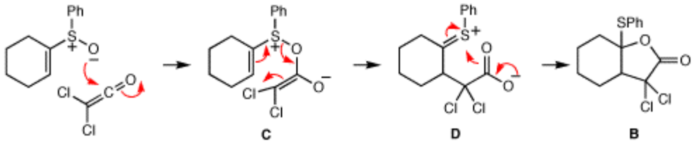
Contributer: **Ian Fleming**
Citation: *J. Am. Chem. Soc.* **1981**, *103*, 7687

The sulfoxide **A** gives the lactone **B** when treated with trichloroacetyl chloride and zinc (J. P. Marino and M. Neisser, *J. Am. Chem. Soc.*, **1981**, *103*, 7687).



Explain this result.

Zinc and an α-chloroacetyl choride is a recipe for making a ketene, in this case dichloroketene. This very electrophilic intermediate is attacked by the oxygen atom of the sulfoxide to give the zwitterion **C**. A [3,3]-sigmatropic rearrangement of this intermediate establishes the C-C bond in the intermediate **D**, and the charges can now cancel in the formation of the O-C bond.



For a different consequence from the reaction of a sulfoxide with dichloroketene, see Problem769, which comes from the same research group.

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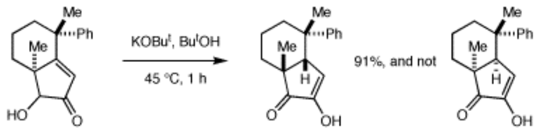
## Problem Answers

### Problem 788

Contributer: **Ian Fleming**
Citation: *J. Org. Chem.* **1970**, *35*, 570

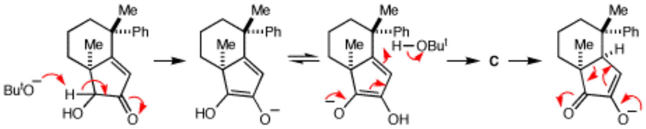
In the base-catalyzed isomerization of the α-hydroxyketone **A** to the enol **B** of an α-diketone, Ireland found that the stereochemistry at the methyl-bearing carbon had unexpectedly changed (R. E. Ireland, P. S. Grand, R. E. Dickerson, J. Bordner and D. R. Rydjeski, *J. Org. Chem.*, **1970**, *35*, 570).



**A** **B** **C**

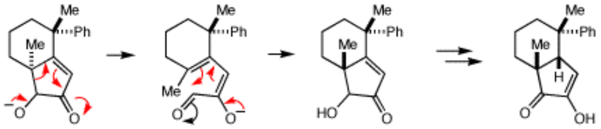
Ireland separately prepared the ketone **C**, which he had expected, and found that this was stable to the reaction conditions. Bearing in mind that **C** was not an intermediate, explain both how and why this isomerization occurred.

The expected pathway to give the isomer **C** was by enolate formation **D**, followed by reprotonation **E**. This might have undergone ring-opening and reclosure. The opening can be drawn as it is in **F**, but it is essentially electrocyclic. It can be expected to be conrotatory in one sense in the opening and in the other sense reclosing. Evidently the formation of the medium-sized ring, although reasonable, required more energy than was available.



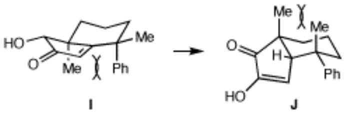
**D** **E** **F**

Instead, the ring-opening step must have been a reverse conjugate aldol reaction **G**, followed by its forward reaction **H** taking place on the other side of the six-membered ring. This is also electrocyclic in nature, and can be expected to have taken place in one conrotatory sense in the opening and in the other sense in reclosing. Only then does the sequence of enolate formation and reprotonation similar to **D** and **E** above give the enol **B** of the α-diketone.



**G** **H** **B**

As to *why* it takes place: The net result is to relieve the 1,3-diaxial clash **I** of the methyl group with the phenyl group in the starting material and to replace it with the less severe 1,3-diaxial clash **J** with another methyl group; meanwhile, the tautomerism shifts the double bond away from the bridgehead and into conjugation with the lone pair of electrons on the hydroxyl oxygen. (A double bond at this bridgehead is not especially unfavorable, but it is effectively a *trans* double bond in a nine membered ring, whereas inside the five-membered ring it is a *cis* double bond within the nine-membered ring.)



**I** **J**

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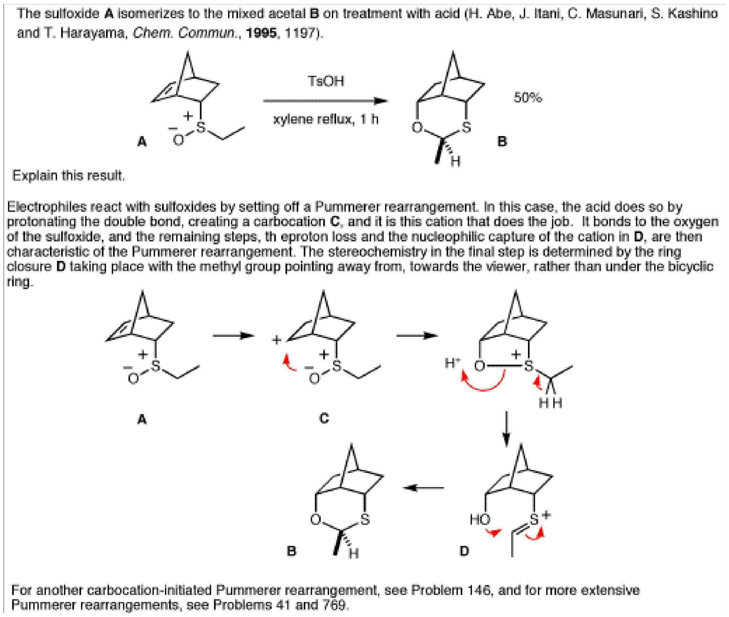
## Problem Answers

### Problem 790

Contributer: **Ian Fleming**
Citation: *Chem. Commun.* **1995**, 1197



The sulfoxide **A** isomerizes to the mixed acetal **B** on treatment with acid (H. Abe, J. Itani, C. Masunari, S. Kashino and T. Harayama, *Chem. Commun.*, **1995**, 1197).

A
TsOH
xylene reflux, 1 h
B
50%

Explain this result.

Electrophiles react with sulfoxides by setting off a Pummerer rearrangement. In this case, the acid does so by protonating the double bond, creating a carbocation **C**, and it is this cation that does the job. It bonds to the oxygen of the sulfoxide, and the remaining steps, th eproton loss and the nucleophilic capture of the cation in **D**, are then characteristic of the Pummerer rearrangement. The stereochemistry in the final step is determined by the ring closure **D** taking place with the methyl group pointing away from, towards the viewer, rather than under the bicyclic ring.

For another carbocation-initiated Pummerer rearrangement, see Problem 146, and for more extensive Pummerer rearrangements, see Problems 41 and 769.

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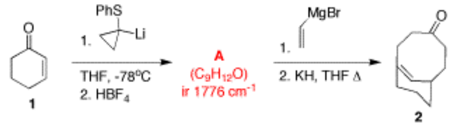
## Problem Answers

### Problem 792

Contributer: **Robert M. Williams**
Citation: *Tetrahedron Lett.* **1980**, *21*, 4547

Kahn reported the interesting pleuromutilin model study shown below (*Tetrahedron Lett.* **1980**, *21*, 4547). Propose a mechanism for the transformation of **1** into "**A**" and the mechanism for the conversion of **A** into **2** and provide the structure for **A**.



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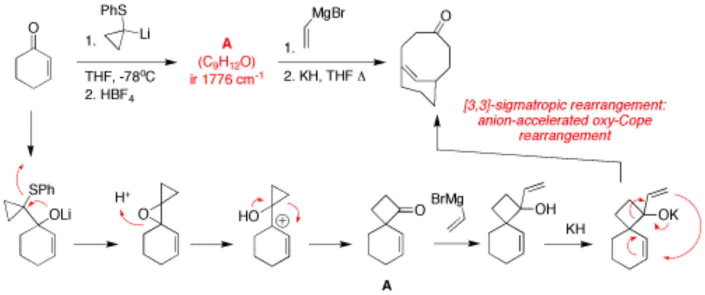

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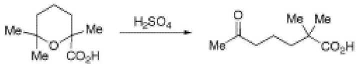
## Problem Answers

## Problem 793

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1960**, *82*, 483-486

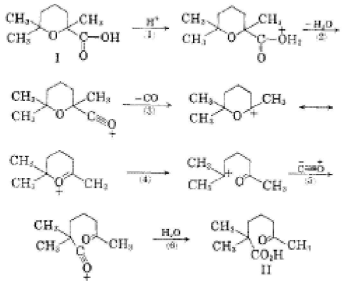
The rearrangement of **1** to **2** was discovered by Rupe and Liechtenhan *(Ber.* **1908**, *41*, 1278). At that time, the transformation attracted attention as a consequence of the *apparent* long-range migration of a methyl group. Meinwald and co-workers *(JACS* **1960**, 82, 483) ultimately provided strong experimental evidence for the mechanism of this rearrangement.



α-cinenic acid (**1**) geronic acid (**2**)

Provide a mechanism for this transformation and suggest experiments that might be carried out to support your proposal.

Chart II



A series of steps involving the loss and subsequent recapture of carbon monoxide is suggested to account for the carboxyl group transfer characteristic of the cinenic acid rearrangement (I → II). This reaction sequence is compatible with all earlier observations, and can be supported by analogies at every stage. The participation of carbon monoxide is indicated by an experiment in which the rearrangement, carried out in the presence of excess carbon monoxide, gave a significantly increased yield of geronic acid (II). Rearrangement in the presence of $C^{14}$-labeled carbon monoxide yielded labeled geronic acid. The possibility that this incorporation is due to exchange of the carboxylic carbon of either the starting material I or the product II with the externally supplied carbon monoxide is excluded by appropriate control experiments.

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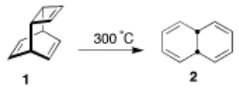
## Problem Answers

### Problem 794

Contributer: **Robert M. Williams**
Citation: *J. Am. Chem. Soc.* **1966**, *88*, 2078-2079

Doering and Rosenthal reported the interesting conversion of Nenitzescu's hydrocarbon (**1**) to dihydro-naphthalene (**2**). Provide a mechanistic rationalization for this transformation. (Reference: Doering, W.v.E.; Rosenthal, J.W., *J.Am.Chem. Soc.* **1966**, *88*, 2078-2079)



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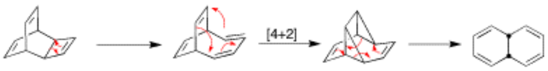

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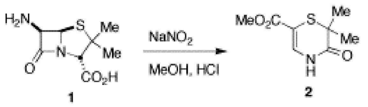
## Problem Answers

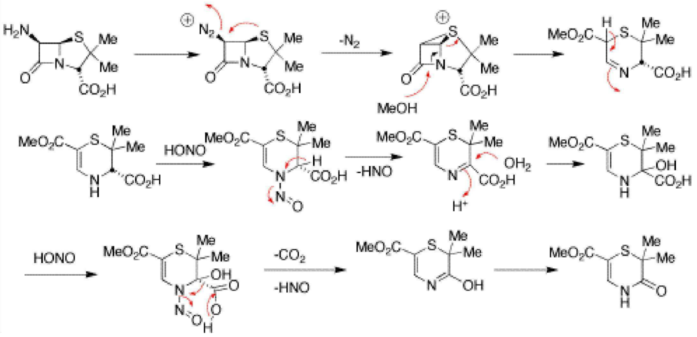
### Problem 795

Contributer: **Robert M. Williams**
Citation: *Tetrahedron Lett.* **1967**, 941-945

Treatment of 6-amino-penicillanic acid (**1**) with sodium nitrite in aqueous methanolic HCl, leads to the interesting heterocycle, 2,3-dihydro-1,4-thaizin-3-one (**2**). Provide a mechanistic rationalization.
(Reference: Stoodley, R.J. *Tetrahedron Lett.* **1967**, 941-945)



*Answer:*



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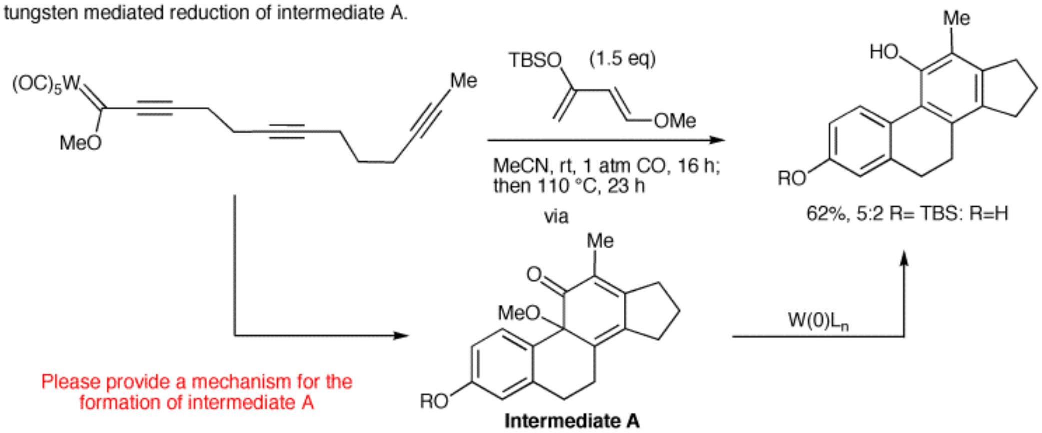
## Problem Answers

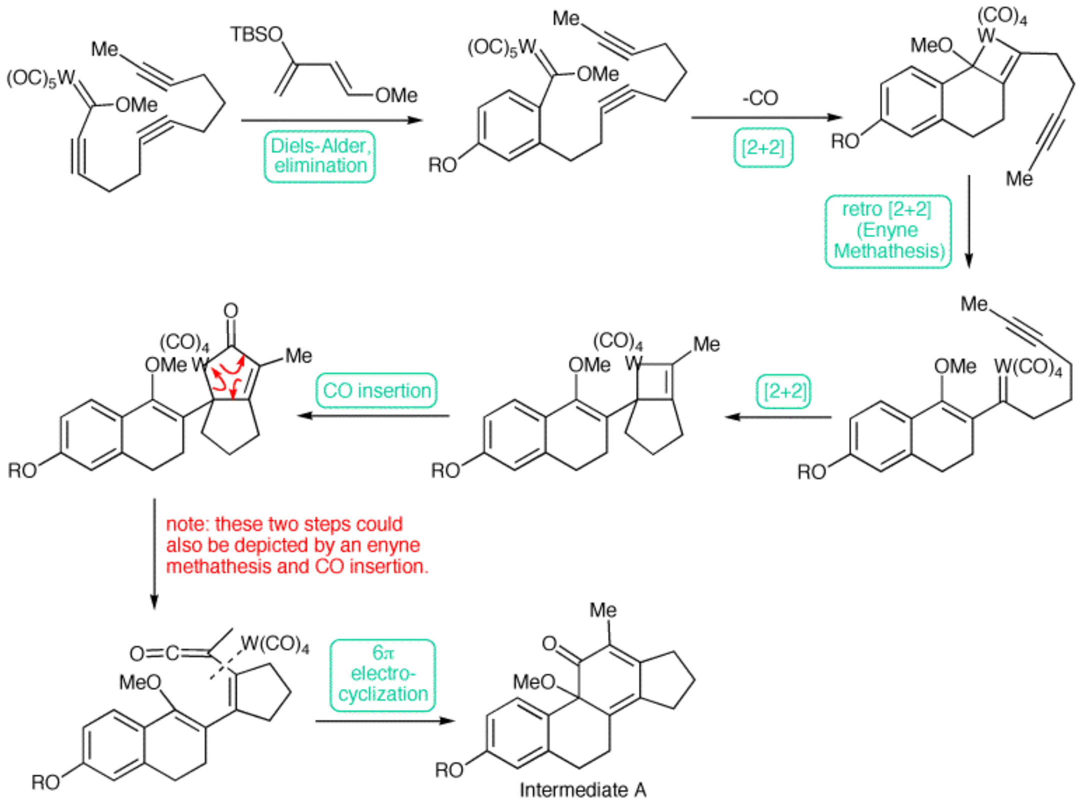
### Problem 796

Contributer: **Dan O'Malley**
Citation: *J. Am. Chem. Soc.* **1994**, *116*, 7616

In their studies on tungsten carbonyl chemistry, Wulff and co-workers discovered a way to construct all four rings of the steroid skeleton in a single cascade (*JACS*, **1991**, *113*, 9873, *JACS*, **1994**, *116*, 7616). The final step of the reaction is the tungsten mediated reduction of intermediate A.



Please provide a mechanism for the formation of intermediate A



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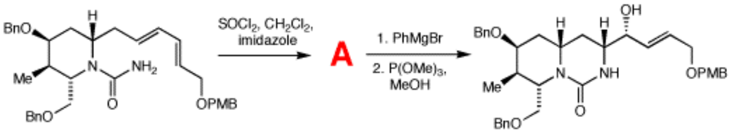
## Problem Answers

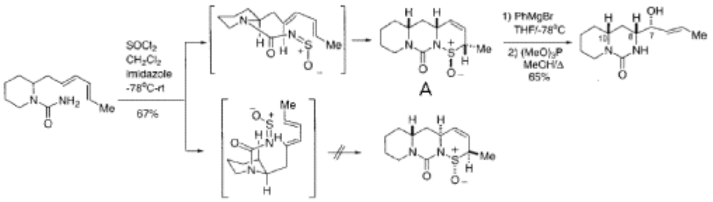
## Problem 812

Contributer: **Achanta Srinavas**
Citation: *J. Am. Chem. Soc.* **2002**, *124*, 3939

As a pivotal step in the synthesis of the freshwater cyanobacterial hepatoxin cylindrospermopsin, Weinreb and co-workers carried out the following transformation (*JACS*, **2002**, *124*, 3939).



Provide a mechanism for the overall transformation and identify **intermediate A**.



The important cycloaddition step is the reaction of the *N*-sulfinyl moiety in a Diels-Alder reaction. This methodology has been reviewed by Weinreb (*Acc Chem. Res.* **1988**, *21*, 313).

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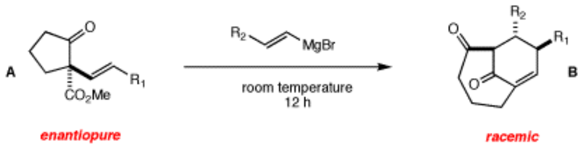
## Problem Answers

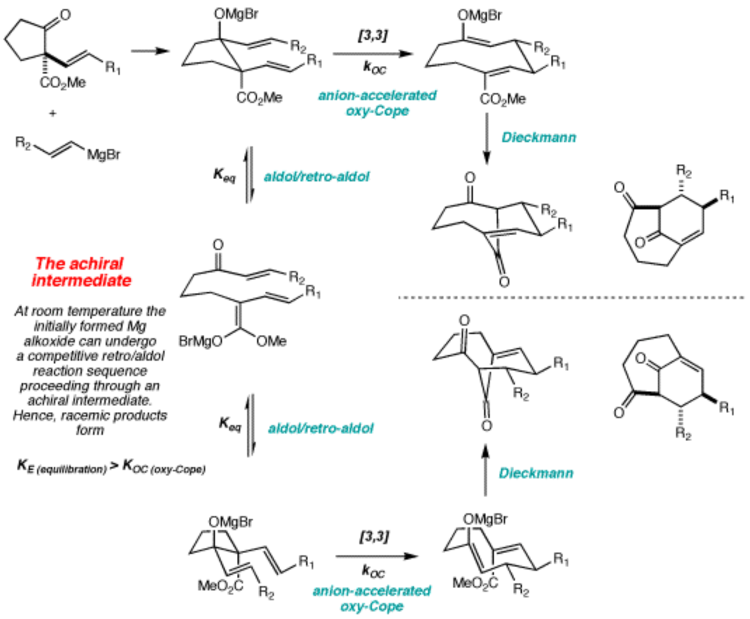
### Problem 813

Contributer: **Regan Thomson**
Citation: *Angew. Chem.* **2005**, *44*, 2259

The key step in Shair's total synthesis of CP-263-114 involved a one-pot synthesis of the bridged bicyclic system using a cascade sequence initiated by a Grignard addition to a β-keto ester. During the course of these studies it was found that if the reaction of enantiopure β–keto ester **A** was allowed to proceed at room temperature for 12 h then the product **B** was obtained as a single diastereomer but as a *racemic mixture.*



Using clear three-dimensional drawings provide an overall mechanism for the transformation shown above that accounts for both the observed diasteroselectivity as well as the formation of the product as a racemate.



*The achiral intermediate*

*At room temperature the initially formed Mg alkoxide can undergo a competitive retro/aldol reaction sequence proceeding through an achiral intermediate. Hence, racemic products form*

$K_{E\ (equilibration)} > K_{OC\ (oxy\text{-}Cope)}$

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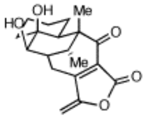
## Problem Answers

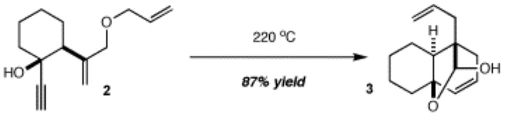
### Problem 815

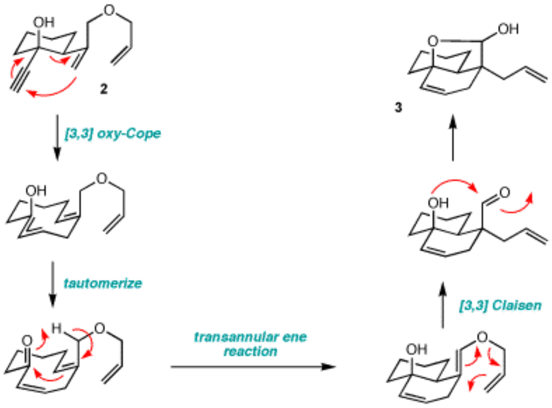
Contributer: **Jillian Spangler**
Citation: *Organic Lett.* **2005**, *7*, 4589

As part of a strategy directed towards the synthesis of tetradecamycin **(1)**, Warrington and Barriault carried out the thermally induced rearrangement of **2** to synthesize the *trans*-decalin system **3** (*Org. Lett.* **2005**, *7*, 4589). Using clear three-dimensional drawings please provide a plausible mechanism for this transformation that is in accordance with the observed stereochemical outcome.



tetradecamycin (**1**)





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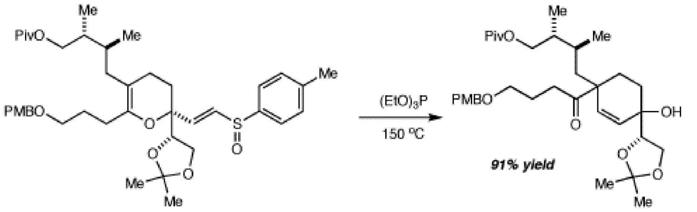
## Problem Answers

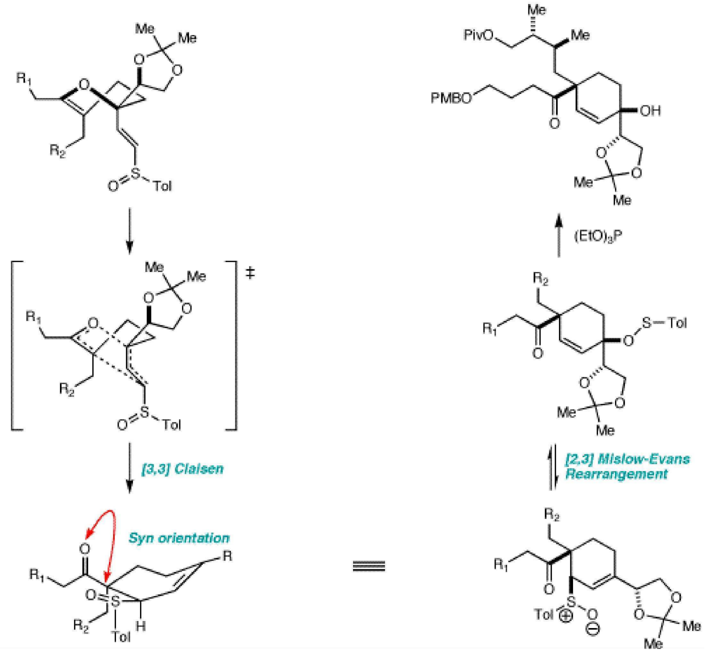
### Problem 816

Contributer: **Regan Thomson**
Citation: *Organic Lett.* **2005**, *7*, 1629

As part of a program directed toward the synthesis of the pinnatoxins, Pelc and Zakarian reported the single-pot conversion of sulfone **A** into cyclohexene **B** (*OL*, **2005**, *7*, 1629). Using clear three-dimensional representations please provide a concise mechanism for this transformation and predict the relative stereochemical outcome.



**Answer**



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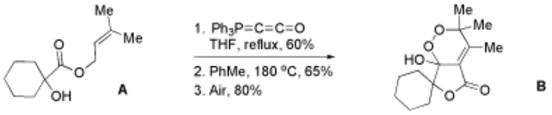
# Problem Answers

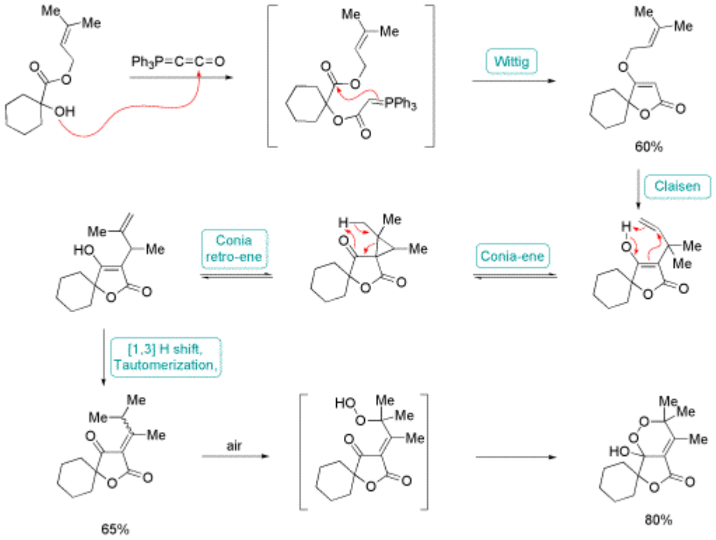
## Problem 822

Contributer: **Christos Mitsos**
Citation: *J. Chem. Soc. Perkin Trans 1* **2003**, *68*, 9827-9830

Schobert and co-workers recently reported an interesting series of events when reacting prenyl ester **A** under the given conditions (R. Schobert *et al*, *Tetrahedron Lett.* **2001**, *42*, 4561-4564; R. Schobert *et al*, *J. Org. Chem.* **2003**, *68*, 9827-9830).



Please delineate a rational mechanism to convert **A** into **B**.



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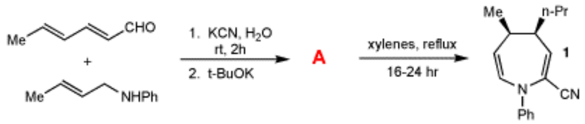
## Problem Answers

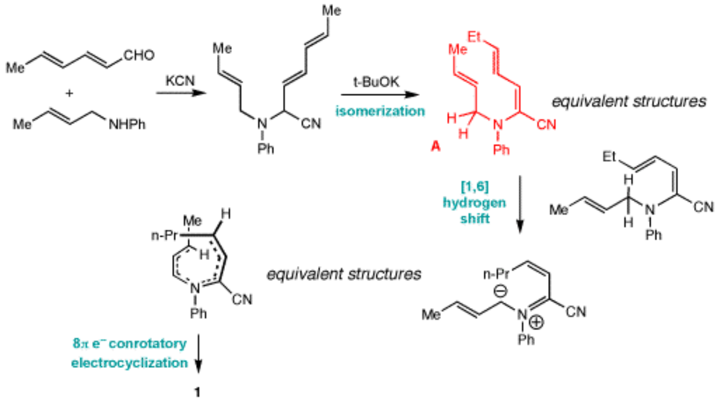
### Problem 828

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1989**, *54*, 481-484

Fang and co-workers reported the following series of transformations (*J. Org. Chem.* **1989**, *54*, 481-484).



The indicated three-step process leads to the production of enamine **1**. Propose a mechanism for the overall transformation that includes the structure of intermediate **A**.



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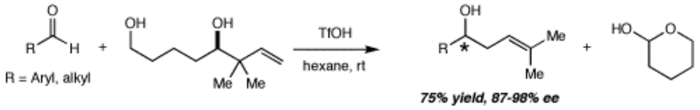
## Problem Answers

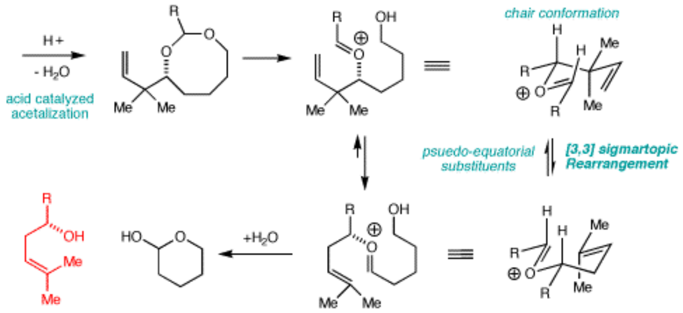
### Problem 829

Contributer: **Regan Thomson**
Citation: *J. Am. Chem. Soc.* **2003**, *125*, 4990

The prenyl group is an essential unit in the biosynthesis of terpene natural products. Due to the large number of natural products that contain this moiety, methods for its selective introduction into molecules are highly useful. Loh and Cheng have descibed a general regioselective and highly enantioselective prenylation of aldehydes, as shown below (*JACS* **2003**, *125*, 4990).



Please provide a general mechanism for this interesting reaction and using clear three-dimensional drawings predict the absolute stereochemical outcome.


H+
- H₂O
acid catalyzed acetalization
R
O
O
Me
Me
R
OH
⊕
O
Me
Me
chair conformation
H
H
Me
R
⊕ O
R
Me
psuedo-equatorial substituents
[3,3] sigmartopic Rearrangement
R
OH
Me
Me
HO
O
+H₂O
R
OH
⊕
O
Me
Me
H
H
Me
R
⊕ O
R
Me

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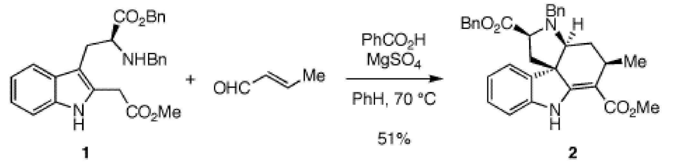
## Problem Answers

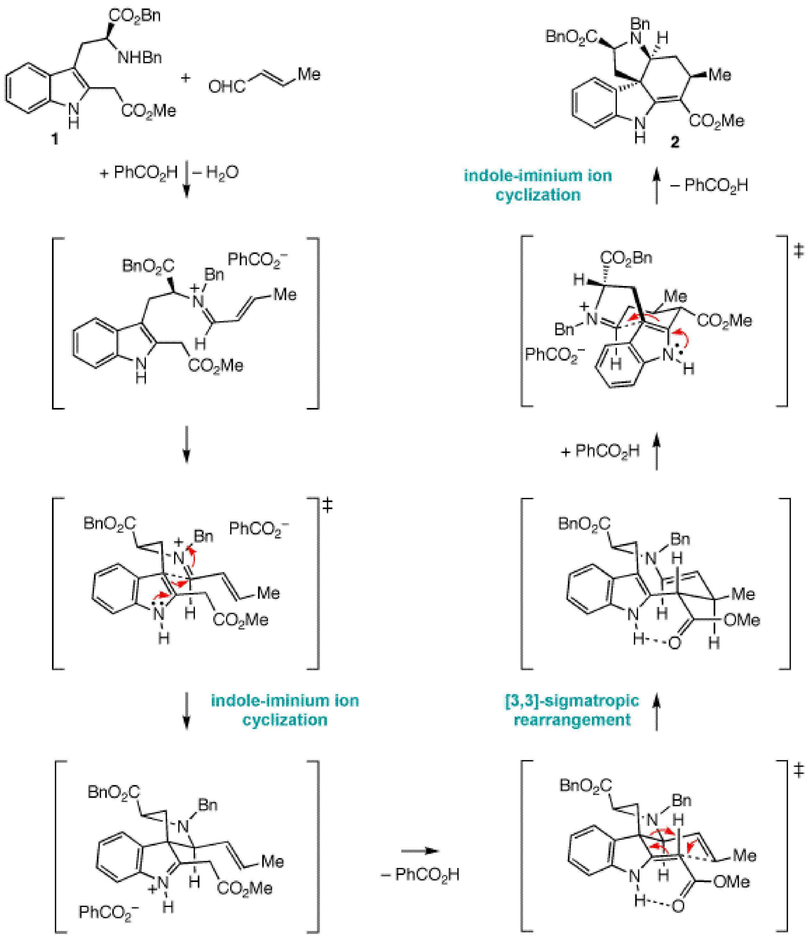
### Problem 831

Contributer: **Mohammad Movassaghi**
Citation: *J. Org. Chem.* **1997**, *62*, 7950-790

Kuehne reported an efficient synthesis of the ABCD ring system of strychnos alkaloids via the conversion of the amino diester **1** to the tetracycle **2** (*JOC* **1997**, *62*, 7950-7960) . Provide a mechanism for this transformation.



**ANSWER:**



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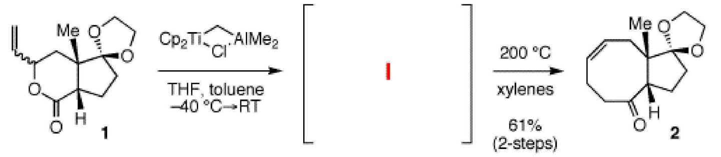
## Problem Answers

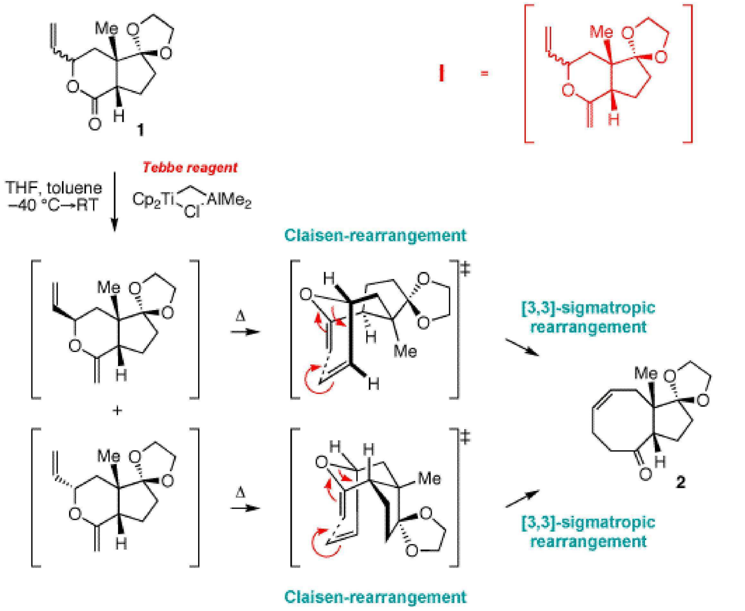
### Problem 832

Contributer: **Mohammad Movassaghi**
Citation: *J. Am. Chem. Soc.* **1993**, *115*, 1676-1683

The following transformation served as a key step in Paquette's synthesis of (+)-ceroplastol I (*JACS* **1993**, *115*, 1676-1683). Identify the intermediate **I** and clearly explain the formation of ketone **2** from lactone **1**.



**ANSWER:**



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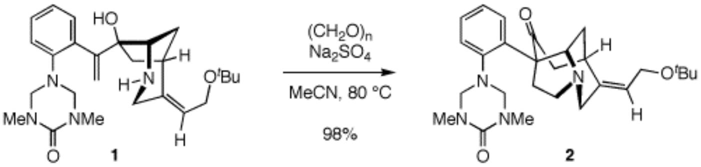
## Problem Answers

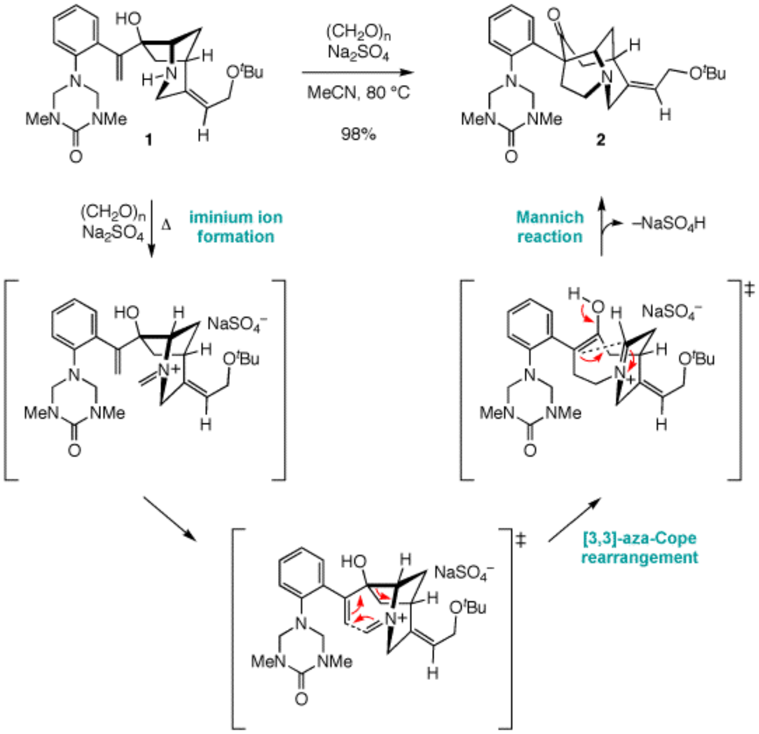
### Problem 833

Contributer: **Mohammad Movassaghi**
Citation: *J. Am. Chem. Soc.* **1993**, *115*, 9293-9294

The following transformation served as a highly effective step in Overman's elegant total synthesis of (–)-strychnine (*JACS* **1993**, *115*, 9293-9294). Provide a mechanism for the conversion of amino alcohol **1** to the ketone **2.**



**ANSWER:**



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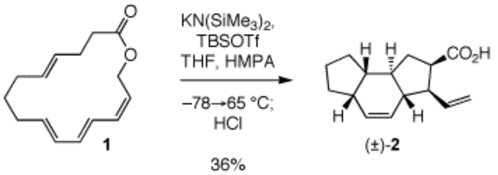
## Problem Answers

### Problem 834

Contributer: **Mohammad Movassaghi**
Citation: *Can J. Chem* **2000**, *78*, 757-771

During studies directed toward the total synthesis of spinosyn A, Roush reported the synthesis of the decahydro-*as*-indacene ring system present in tricycle **2** (*Can. J. Chem.* **2000**, *78*, 757-771). Provide a reasonable mechanism for the conversion of lactone **1** to the carboxylic acid **2**.



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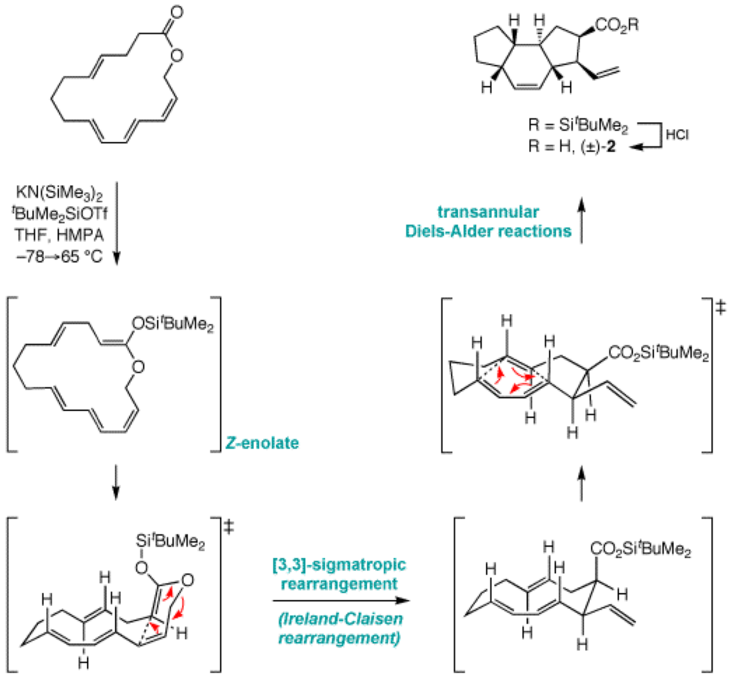

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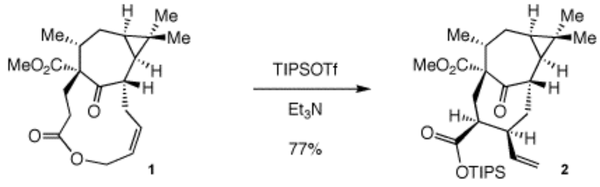
## Problem Answers

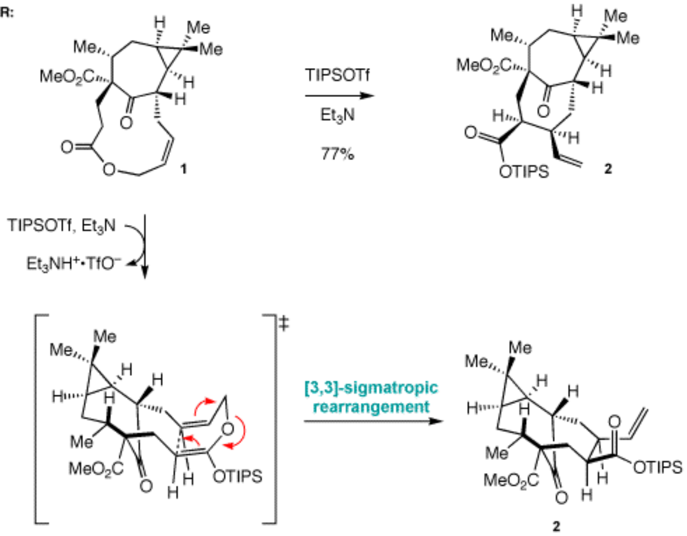
### Problem 835

Contributer: **Mohammad Movassaghi**
Citation: *J. Am. Chem. Soc.* **110**, *110*, 3298-3300

During studies related to the synthesis of ingenol, Funk reported the conversion of lactone **1** to the silyl ester **2** (*JACS* **1988**, *110*, 3298-3300). Provide a mechanism for this transformation and clearly account for the observed stereochemistry in the product **2**.



**ANSWER:**



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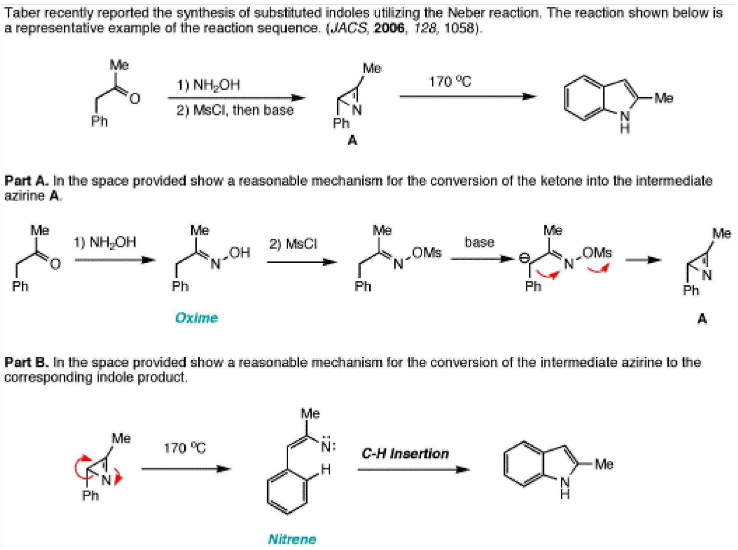
## Problem Answers

### Problem 837

Contributer: **Keith Fandrick**
Citation: *J. Am. Chem. Soc.* **2006**, *ASAP*,



Taber recently reported the synthesis of substituted indoles utilizing the Neber reaction. The reaction shown below is a representative example of the reaction sequence. (*JACS*, **2006**, *128*, 1058).

**Part A.** In the space provided show a reasonable mechanism for the conversion of the ketone into the intermediate azirine **A**.

**Part B.** In the space provided show a reasonable mechanism for the conversion of the intermediate azirine to the corresponding indole product.

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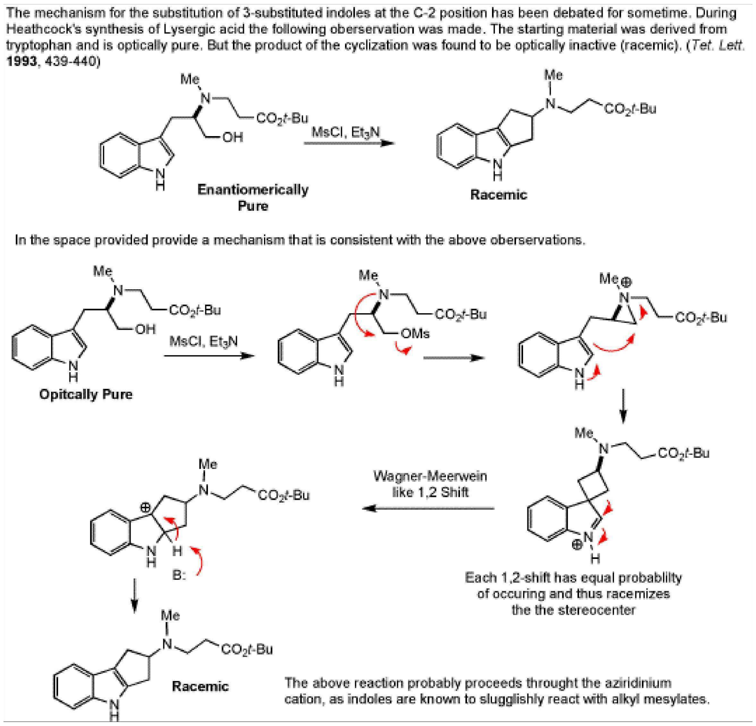
## Problem Answers

### Problem 839

Contributer: **Keith Fandrick**
Citation: *Tetrahedron Lett.* **1993**, 439



The mechanism for the substitution of 3-substituted indoles at the C-2 position has been debated for sometime. During Heathcock's synthesis of Lysergic acid the following oberservation was made. The starting material was derived from tryptophan and is optically pure. But the product of the cyclization was found to be optically inactive (racemic). (*Tet. Lett.* **1993**, 439-440)

In the space provided provide a mechanism that is consistent with the above oberservations.

Each 1,2-shift has equal probablilty of occuring and thus racemizes the the stereocenter

The above reaction probably proceeds throught the aziridinium cation, as indoles are known to slugglishly react with alkyl mesylates.

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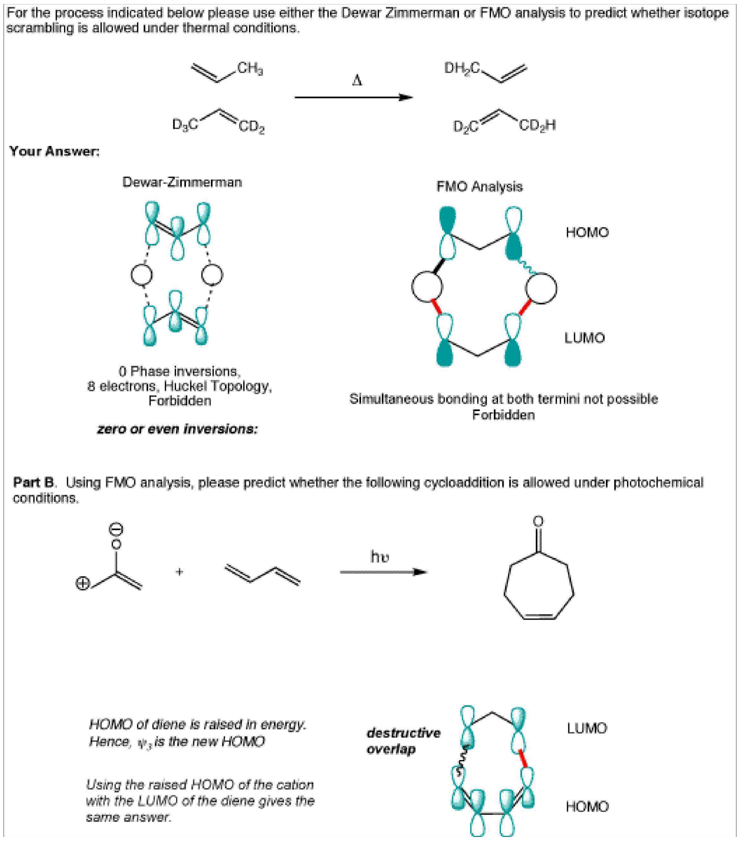
## Problem Answers

## Problem 846

Contributer: **Pavel Nagorny**
Citation:


For the process indicated below please use either the Dewar Zimmerman or FMO analysis to predict whether isotope scrambling is allowed under thermal conditions.

**Your Answer:**

0 Phase inversions,
8 electrons, Huckel Topology,
Forbidden

***zero or even inversions:***

Simultaneous bonding at both termini not possible
Forbidden

**Part B.** Using FMO analysis, please predict whether the following cycloaddition is allowed under photochemical conditions.

*HOMO of diene is raised in energy. Hence, $\psi_3$ is the new HOMO*

*Using the raised HOMO of the cation with the LUMO of the diene gives the same answer.*

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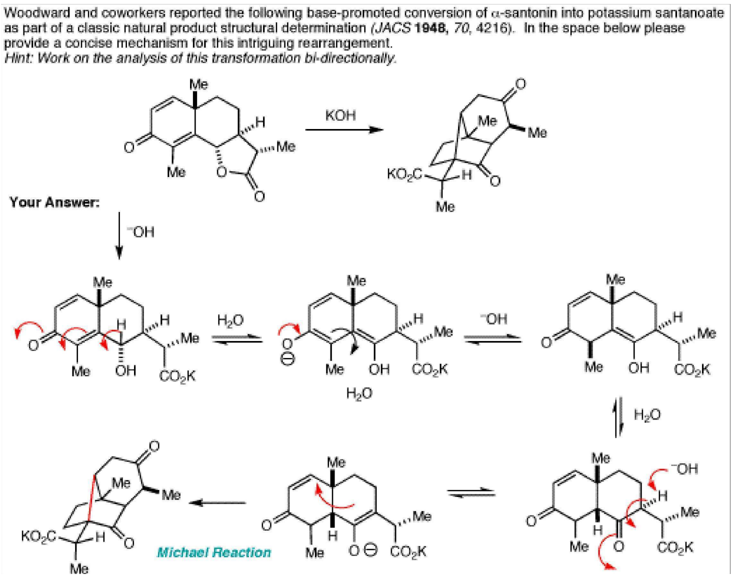
## Problem Answers

### Problem 851

Contributer: **Regan Thomson**
Citation: *J. Am. Chem. Soc.* **1948**, *70*, 4216



Woodward and coworkers reported the following base-promoted conversion of α-santonin into potassium santanoate as part of a classic natural product structural determination (*JACS* **1948**, *70*, 4216). In the space below please provide a concise mechanism for this intriguing rearrangement.
*Hint: Work on the analysis of this transformation bi-directionally.*

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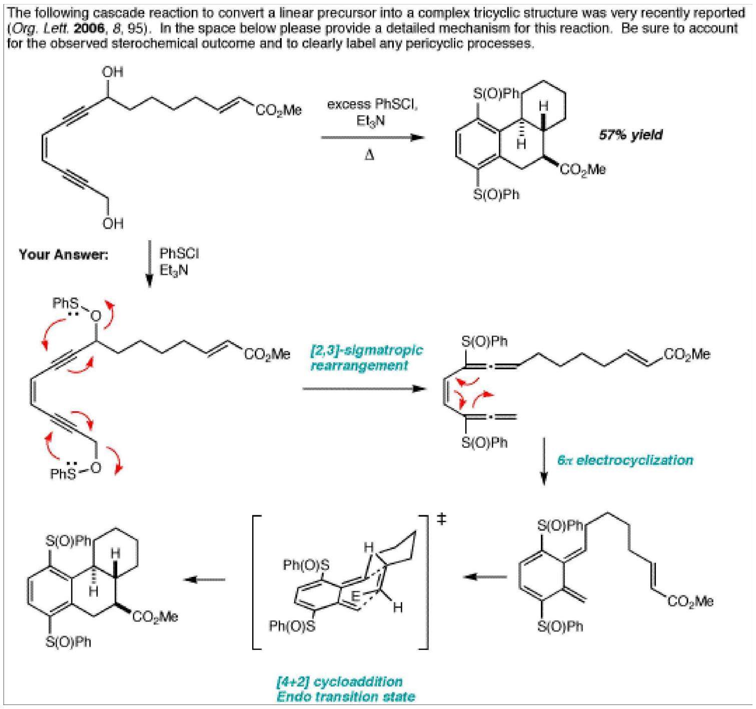
## Problem Answers

**Problem 853** Contributer: **David A. Evans**
Citation: *Organic Lett.* **2006**, *8*, 95



The following cascade reaction to convert a linear precursor into a complex tricyclic structure was very recently reported (*Org. Lett.* **2006**, *8*, 95). In the space below please provide a detailed mechanism for this reaction. Be sure to account for the observed sterochemical outcome and to clearly label any pericyclic processes.

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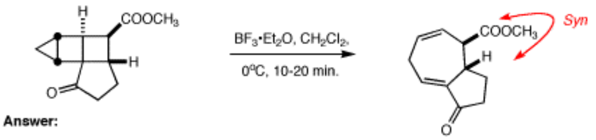
## Problem Answers

### Problem 854

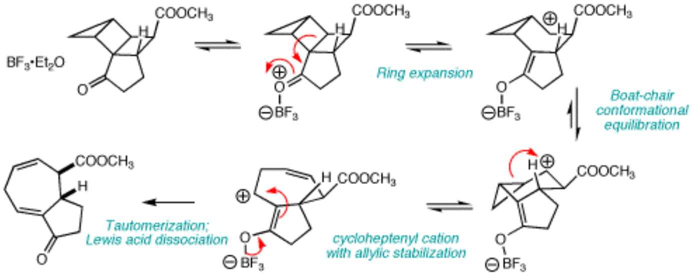
Contributer: **David A. Evans**
Citation: *Organic Lett.* **2005**, *7*, 5785

Snapper and co-workers have recently identified a mild, Lewis acid-mediated fragmentation of cyclobutane-containing adducts as a rapid entry into bicyclo[5.3.0]decane ring systems (*Org. Lett.* **2005**, *7*, 5785). They also noted that the stereochemical outcome of the acid-mediated fragmentations in such systems is complementary to the observed thermal ring expansions.

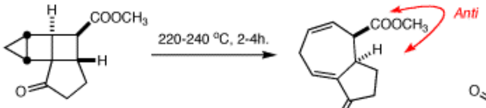
**Part 1.** Please provide a plausible mechanism for the following Lewis acid-mediated transformation.



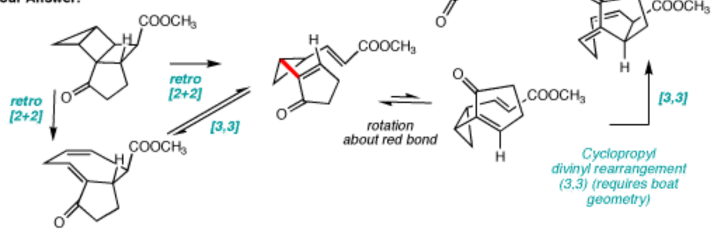
**Your Answer:**


COOCH3
H
BF3•Et2O
O
COOCH3
H
⊕
O
⊖BF3
Ring expansion
⊕
COOCH3
H
O
⊖BF3
Boat-chair conformational equilibration
H⊕
COOCH3
O
⊖BF3
cycloheptenyl cation with allylic stabilization
H COOCH3
⊕
O
⊖BF3
Tautomerization; Lewis acid dissociation
COOCH3
H
O

**Part 2.** Propose a mechanism that rationalizes the complementry stereochemical outcome of the following thermal rearrangement.



**Your Answer:**



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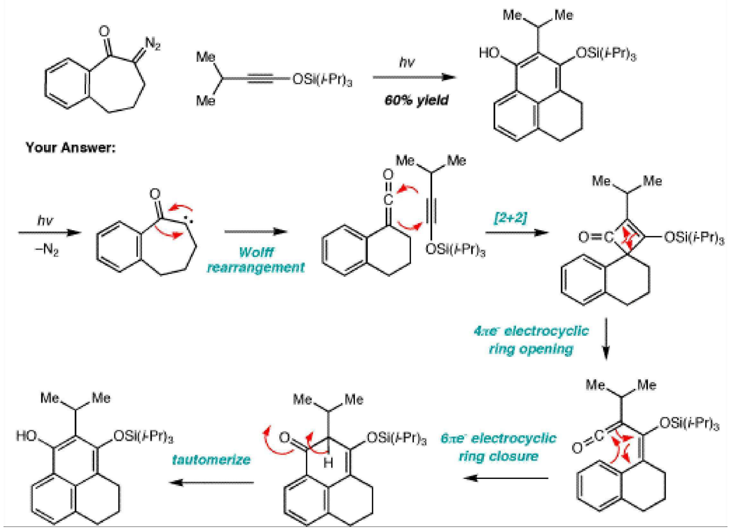
## Problem Answers

### Problem 855

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1990**, *112*, 3093

As part of a study directed towards the synthesis of the natural product Hyellazole, Danheiser and coworkers developed a clever route to the synthesis of complex fused polycyclic structures (*JACS* **1990**, *112*, 3093). Please provide a mechanism for the following rearrangement. Be sure to label all relevant pericyclic rarrangements.



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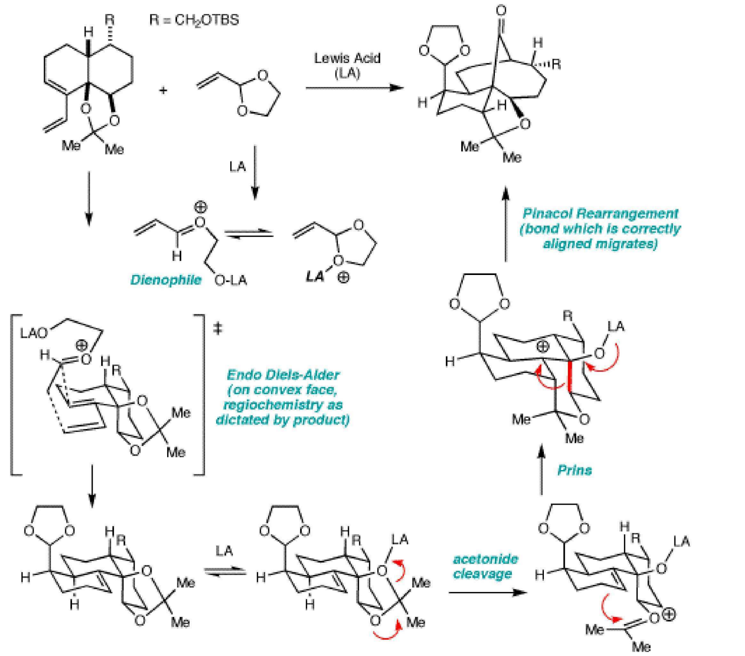
## Problem Answers

**Problem 856** Contributer: **Meredth McGowen**
Citation: *Organic Lett.* **2005**, *7*, 5921

Barriault recently published the following Lewis-acid mediated reaction cascade as a strategy to rapidly assemble highly functionalized bicycloalkanones (*Org. Lett.* **2005**, *7*, 5921). Using clear 3D representations, please provide a mechanism that includes a rationalization for the relative stereochemistry observed in the product.


R = CH2OTBS
Lewis Acid (LA)
LA
Dienophile
O-LA
LA ⊕
Pinacol Rearrangement (bond which is correctly aligned migrates)
LAO
‡
Endo Diels-Alder (on convex face, regiochemistry as dictated by product)
Prins
acetonide cleavage
Me
H
R
O

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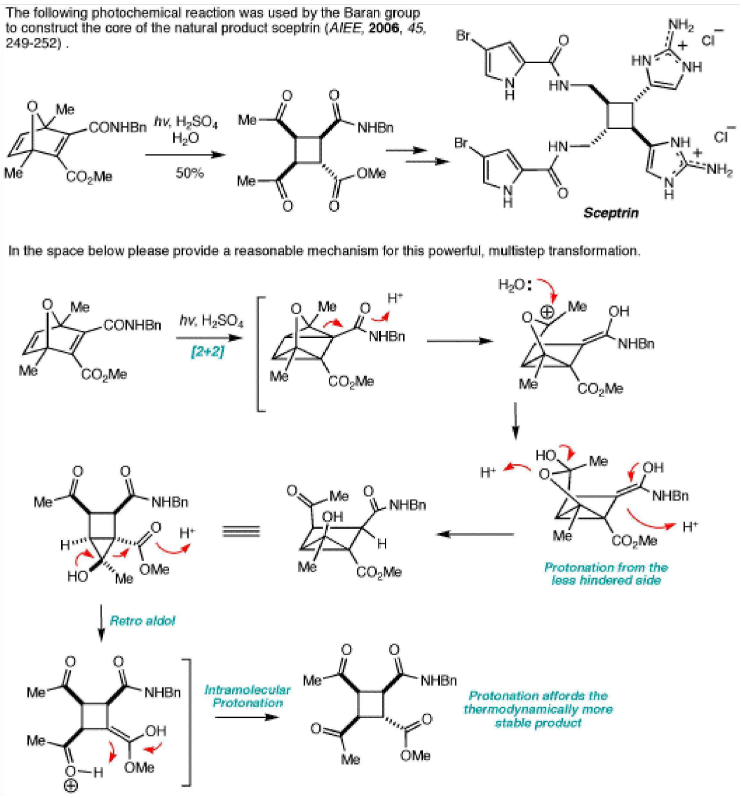
## Problem Answers

**Problem 857** Contributer: **David A. Evans**
Citation: *Angew. Chem.* **2006**, *45*, 249-252



The following photochemical reaction was used by the Baran group to construct the core of the natural product sceptrin (*AIEE*, **2006**, *45*, 249-252) .

In the space below please provide a reasonable mechanism for this powerful, multistep transformation.

hν, $H_2SO_4$
$H_2O$
50%
Sceptrin
hν, $H_2SO_4$
[2+2]
Protonation from the less hindered side
Retro aldol
Intramolecular Protonation
Protonation affords the thermodynamically more stable product

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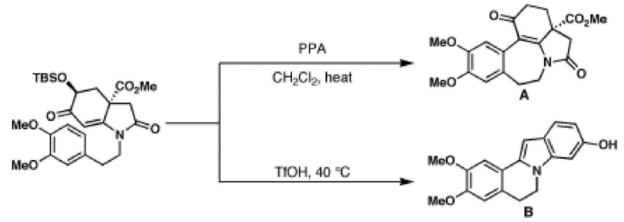
## Problem Answers

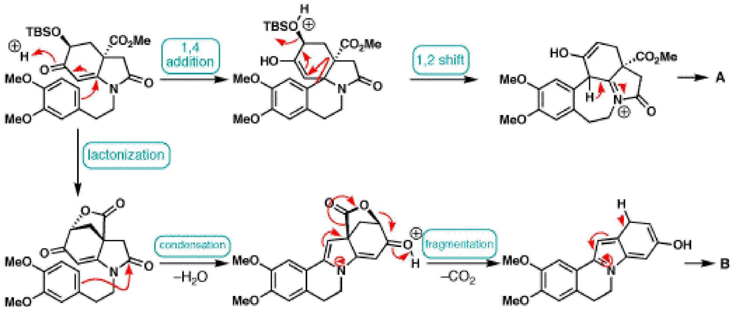
### Problem 861

Contributer: **David Lin**
Citation: *Organic Lett.* **2006**, *8*, 601-604

While developing a route to the synthesis of Erythrina alkaloids, Padwa and colleagues encountered the following transformations (Org. Lett. **2006**, *8*, 601-604).



Propose a mechanism for both observed rearrangements.



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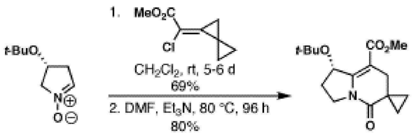
## Problem Answers

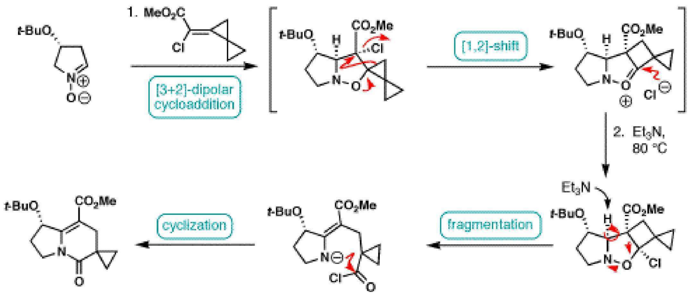
### Problem 862

Contributer: **Ryan Shenvi**
Citation: *J. Org. Chem.* **2006**, *71*, 2417-2423

Alberto Brandi and co-workers recently reported the rearrangement of isoxazolidines to enantiopure indolizinones by way of the chemistry of halomethylcyclopropanes (*J. Org. Chem.*, **2006**, *71*, 2417-2423).



Please delineate a mechanism to arrive at the final product.



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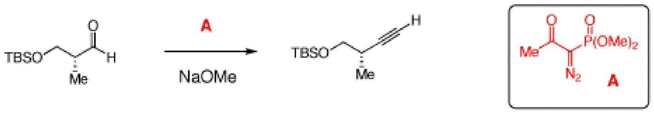
## Problem Answers

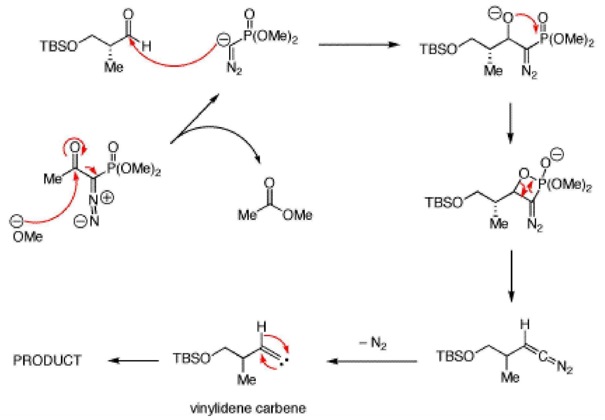
## Problem 866

Contributer: **Karl Scheidt**
Citation: *J. Am. Chem. Soc.* **2005**, *127*, 17921

In the total synthesis of Amphidinolide P (*J. Am. Chem. Soc.* **2005**, *127*, 17921-17937), Trost and coworkers employed the Bestmann reagent (**A**) to synthesize the shown alkyne. Provide a mechanism for this step.



**Your Answer**



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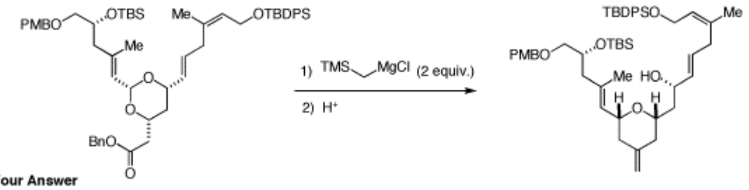
# Problem Answers

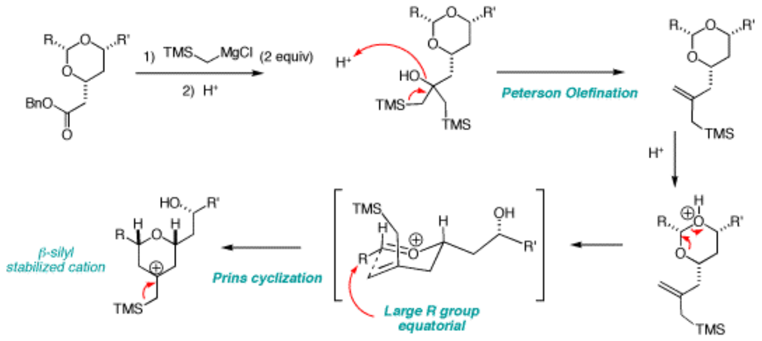
## Problem 869

Contributer: **Karl Scheidt**
Citation: *Angew. Chem.* **2005**, *44*, 3485-3488

Floreancig and co-workers, in their synthesis of the anti-cancer natural product (+)-dactylolide, carried out the following step (*Angew. Chem. Int. Ed.* **2005**, *44*, 3485-3488). Please provide a mechanism which rationalizes the observed stereochemistry.



**Your Answer**



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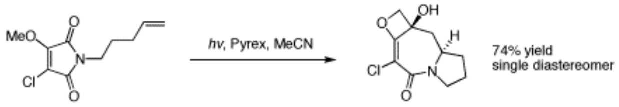
## Problem Answers

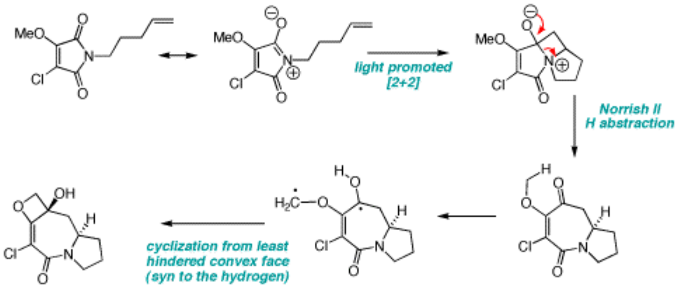
### Problem 870

Contributer: **Karl Scheidt**
Citation: *Organic Lett.* **2004**, *6*, 1481-1484

Booker-Milburn and coworkers have disclosed the following route to oxetanes from alkoxy-substituted maleimides (*Org. Lett.* **2004**, *6*, 1481-1484). Please provide a mechanistic pathway leading to the major product. HINT 1: Consider the amide bond resonance structures of the starting material. HINT 2: Your mechanism should include a Norrish type II cleavage.



**Your Answer**



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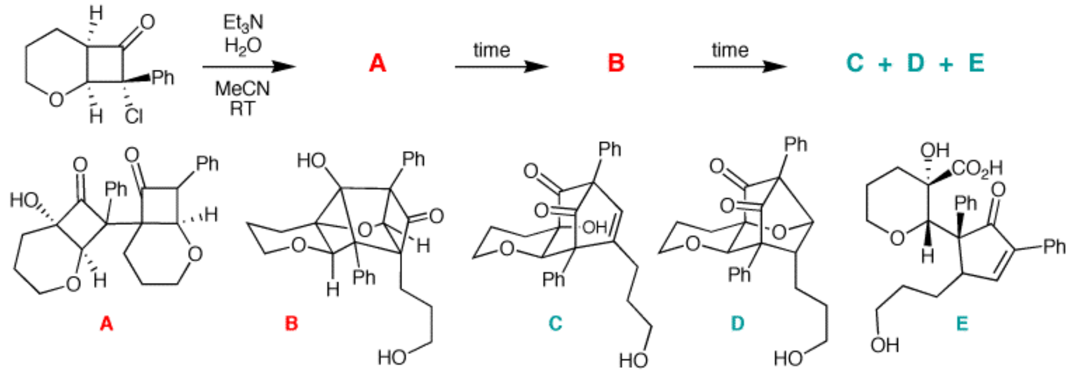
## Problem Answers

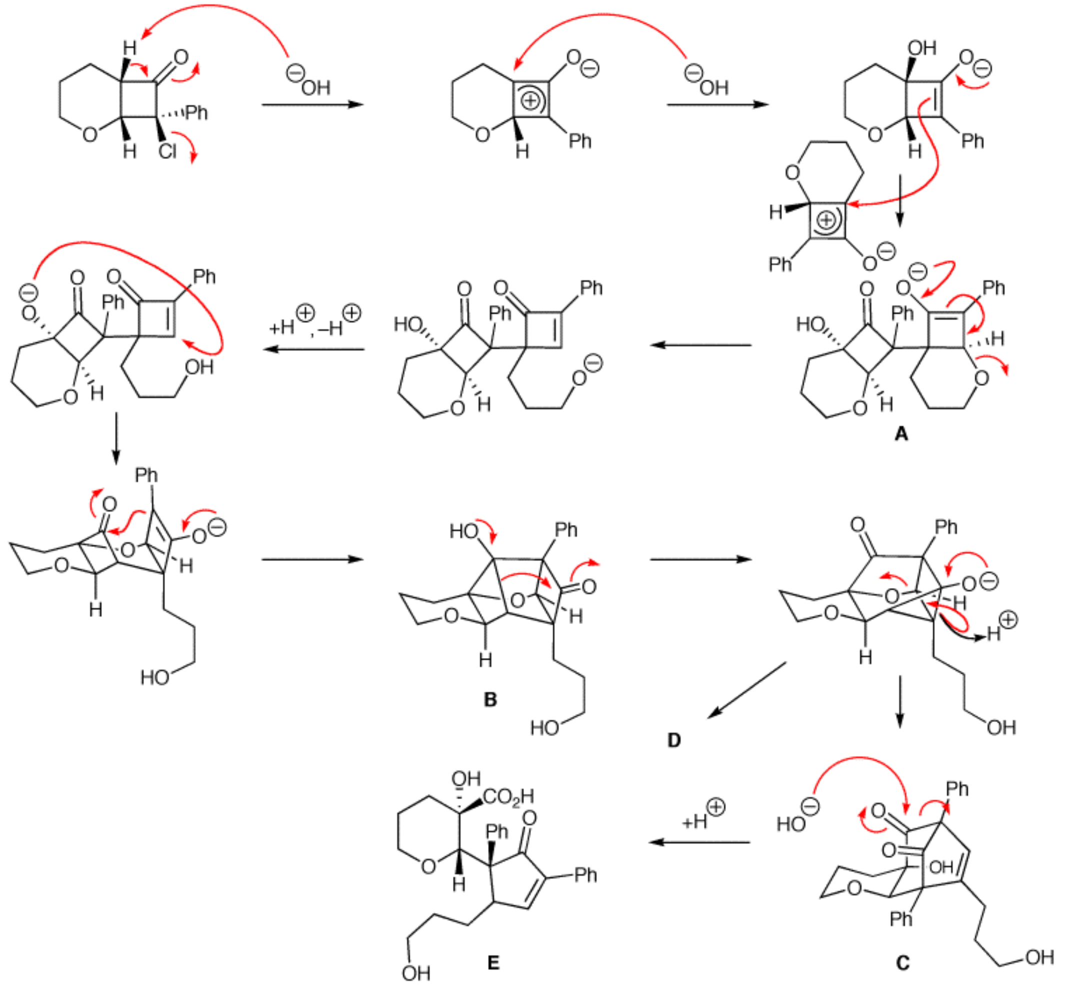
### Problem 872

Contributer: **Jeremy Richter**
Citation: *J. Org. Chem.* **1993**, *58*, 5699-5701

In examining the chemistry of the of chlorobicyclooctanone shown below, the authors discovered several unique rearrangements (*J. Org. Chem.* **1993**, *58*, 5699 – 5701).



Please propose mechanisms for the formation of all five products.



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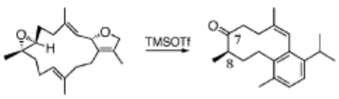
## Problem Answers

### Problem 874

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2006**, *88*, 2957-2960

Treatment of sarcophytoxide with TMSOTf afforded the illustrated aromatic ketone as an unusual cyclization product. *Org. Lett* **2006**, *8*, 2957-2960.

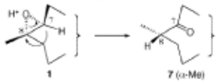
Provide a mechanism for this transformation.



sarcophytoxide 60% ee

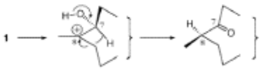
The first step is an epoxide-ketone rearrangement which the authors conclude is non-sterepspecific (Eq A and B). The subsequent steps are illustrated in Scheme 3 below as provided by the authors.

Equation A



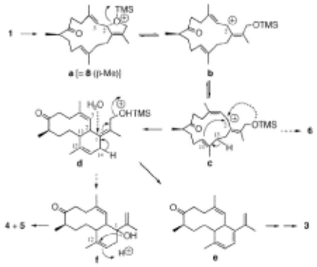
1 7 (α-Me)

Equation B



8 (β-Me)

**Scheme 3**



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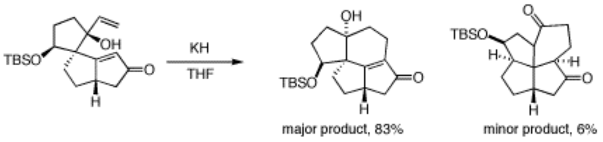
## Problem Answers

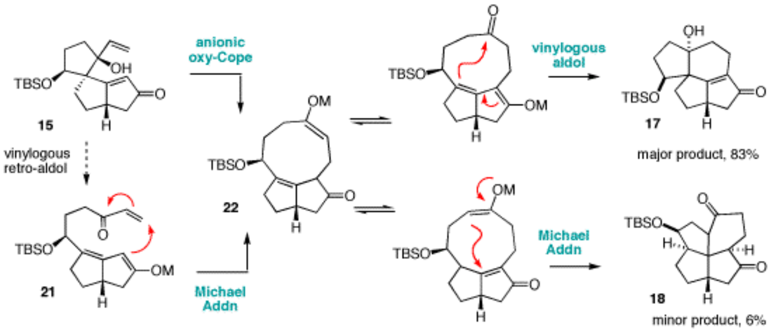
### Problem 875

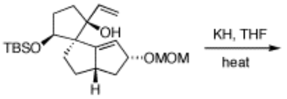
Contributer: **David A. Evans**
Citation: *Organic Lett.* **2006**, *88*, 3195-3198

Burnell and Thornton have recently disclosed the following base induced transformation (*Org. Lett.* **2006**, *8*, 3195-3198). The structures of both products were secured by X-ray analysis.



Please provide a rational mechanism leading to the major and minor products.



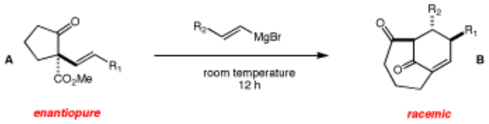


**No observed rearrangement.** From this control experiment, the authors conclude that an anionic oxy-Cope rearrangement is not involved. While this expertiemt is suggestive, it does not rule out the Cope option since the conjugated =O in **15** will have a large impact on the rate of the Cope process. DAE believes to be the case in this instance. For example, see the following publication and the case reported by Shair, prob. 813.

"Regiospecific Quinone Isoprenylation. Examples of Remarkably Facile [3,3] Sigmatropic Processes," Evans, D. A.; Hoffman, J. M., *JACS* **1976,** *98,* 1983-1984

**Problem 813** Shair et al. *Angew, Chemie, Int. Ed.* **2005**, *44*, 2259

The key step in Shair's total synthesis of CP-263-114 involved a one-pot synthesis of the bridged bicyclic system using a cascade sequence initiated by a Grignard addition to a β-keto ester. During the course of these studies it was found that if the reaction of enantiopure β–keto ester **A** was allowed to proceed at room temperature for 12 h then the product **B** was obtained as a single diastereomer but as a *racemic mixture*.



Using clear three-dimensional drawings provide an overall mechanism for the transformation shown above that accounts for both the observed diasteroselectivity as well as the formation of the product as a racemate.

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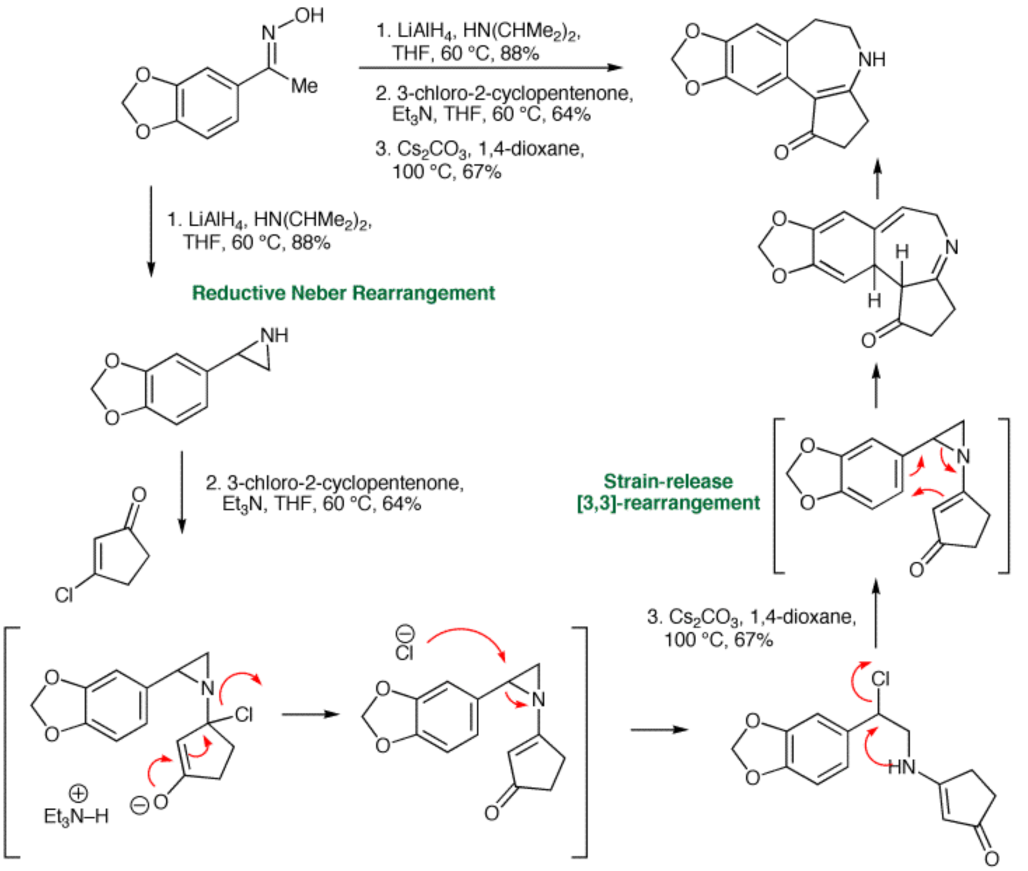
## Problem Answers

### Problem 877

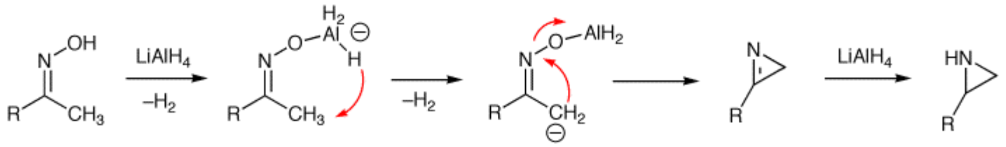
Contributer: **Karl Scheidt**
Citation: *J. Am. Chem. Soc.* **2006**, *128*, ASAP

Gin and co-workers (*JACS* **2006**, *128*, ASAP) recently reported the following set of transformations during the total synthesis of the anti-Leukemia alkaloid (–)-deoxyharrington. Provide the mechanisms for the following series of reactions.

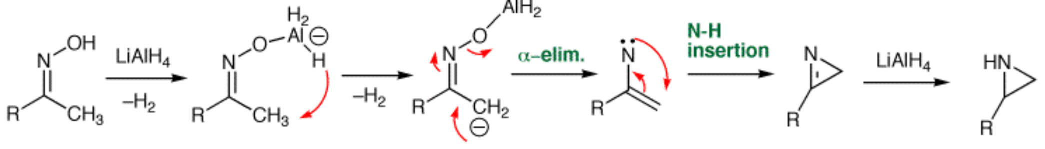

1. LiAlH4, HN(CHMe2)2, THF, 60 °C, 88%
2. 3-chloro-2-cyclopentenone, Et3N, THF, 60 °C, 64%
3. Cs2CO3, 1,4-dioxane, 100 °C, 67%
Reductive Neber Rearrangement
Strain-release [3,3]-rearrangement
Et3N–H

**Reductive Neber Rearrangement**

(a) *Kotera Bull. Chem. Soc. Jap.* ***1973**, 46, 934*



(b) *Alternative Mechanism*



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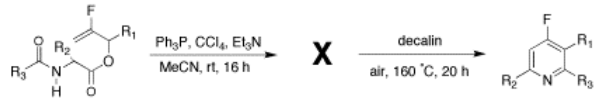
## Problem Answers

### Problem 878

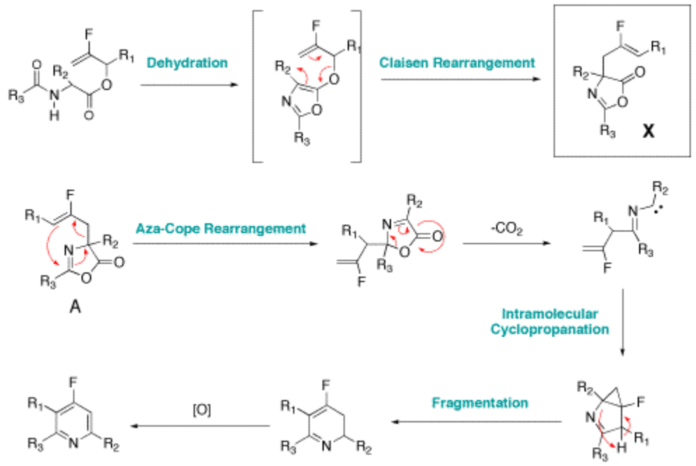
Contributer: **Jun Shi**
Citation: *Synthesis* **2006**, 2058-2096

While developing a synthetic route to 4-Fluoropyridines, Ulrich Wittmann and Colleagues encountered the following transformation (*Synthesis* **2006**, *13*, 2058–2096).



R$_1$=H, R$_2$=Ph, R$_3$=Ph

Please provide a reasonable mechanism for this set of transformations and Identify **X**.



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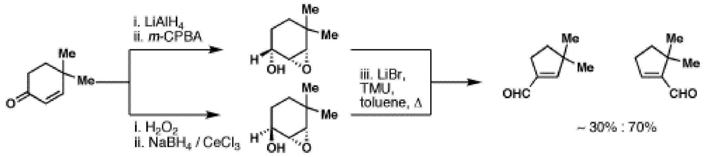
## Problem Answers

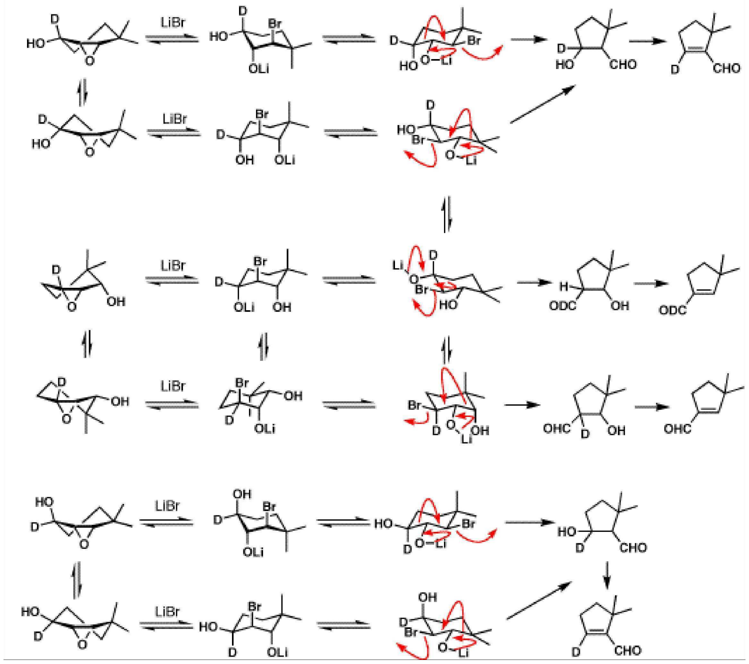
### Problem 895

Contributer: **Moritz Biskup**
Citation: *J. Org. Chem.* **1986**, *51*, 212-217

In studies directed toward the syntheses of terpenes, G. Magnusson *et al.* investigated the preparation α,β-unsaturated cyclopentenals from six-membered precursors (*J.Org.Chem.* **1986**, *51*, 212-217). The reaction was studied in detail and the postulated mechanism rationalizes the observed product formation.



Please provide a plausible mechanism for the formation of the indicated products.



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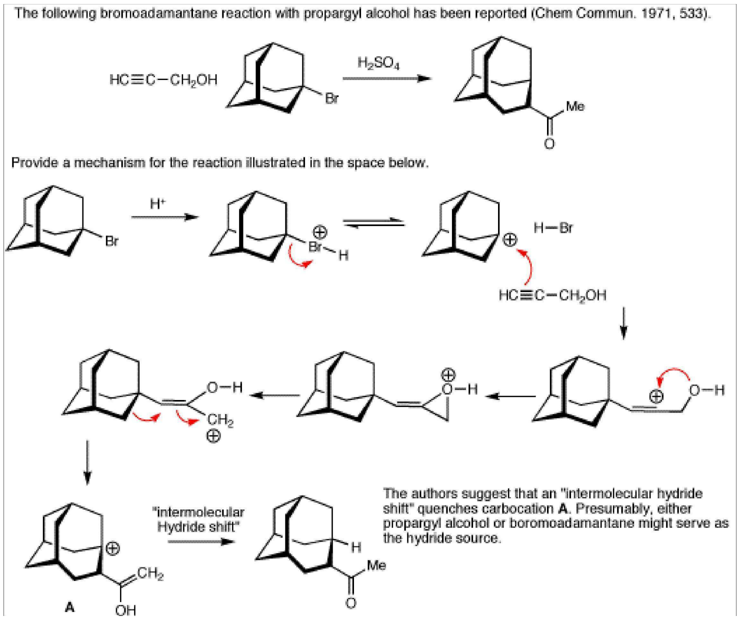
## Problem Answers

### Problem 897

Contributer: **David A. Evans**
Citation: *Chem. Commun.* **1971**, 533



The following bromoadamantane reaction with propargyl alcohol has been reported (Chem Commun. 1971, 533).

Provide a mechanism for the reaction illustrated in the space below.

The authors suggest that an "intermolecular hydride shift" quenches carbocation **A**. Presumably, either propargyl alcohol or boromoadamantane might serve as the hydride source.

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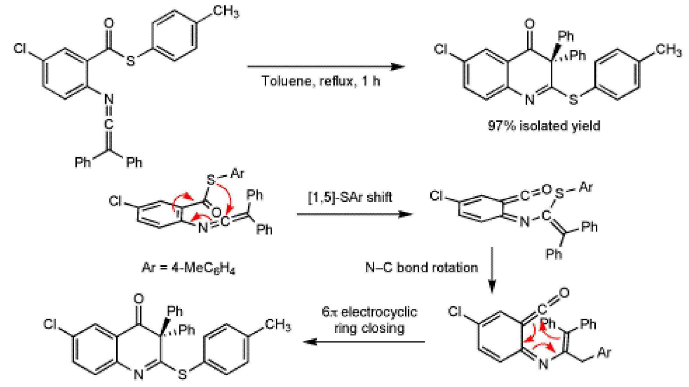
## Problem Answers

### Problem 904

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2006**, *71*, 816

The quinolinone synthesis depicted below was recently reported by Alajarín and coworkers (*J. Org. Chem.* **2006**, *71*, 8126-8139). Please provide a mechanism for this transformation.



Tandem Pseudopericyclic Reactions: [1,5]-X Sigmatropic Shift/6π-Electrocyclic Ring Closure Converting *N*-(2-X-Carbonyl)phenyl Ketenimines into 2-X-Quinolin-4(3*H*)-ones. Alajarín, M.; Ortín, M.-M.; Sánchez-Andrada, P.; Vidal, Á. *J. Org. Chem.* **2006**, *71*, 8126-8139.

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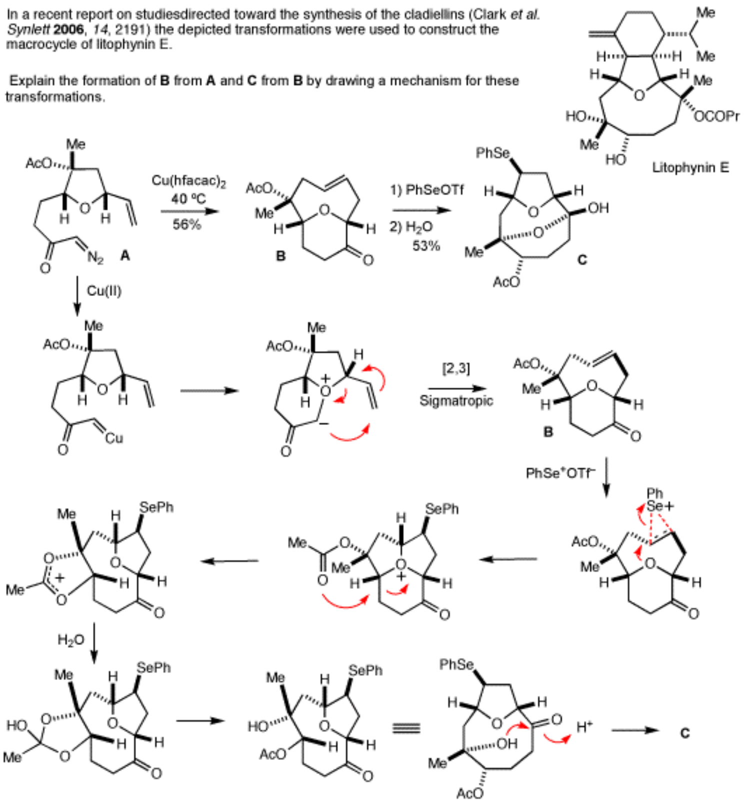
## Problem Answers

### Problem 905

Contributer: **Pavel Nagorny**
Citation: *SynLett* **2006**, *14*, 2191



In a recent report on studiesdirected toward the synthesis of the cladiellins (Clark *et al.* *Synlett* **2006**, *14*, 2191) the depicted transformations were used to construct the macrocycle of litophynin E.

Explain the formation of **B** from **A** and **C** from **B** by drawing a mechanism for these transformations.

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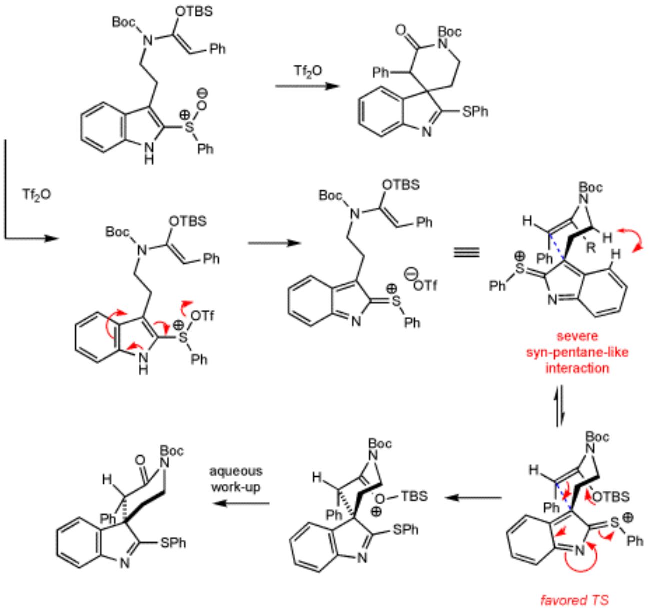
## Problem Answers

### Problem 907

Contributer: **Hyun-Ji Song**
Citation: *Organic Lett.* **2004**, *6*, 1869-1871

In 2004, Feldman and coworker published a construction of 3,3-spirosubstituted oxindoles. (*Org. Lett.* **2004**, *6*, 1869-1871). Provide the reaction mechanism and use it to predict the product relative stereochemistry. Explain the origins of diastereoselectivity using clear 3D drawings.



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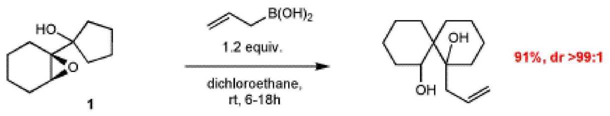
## Problem Answers

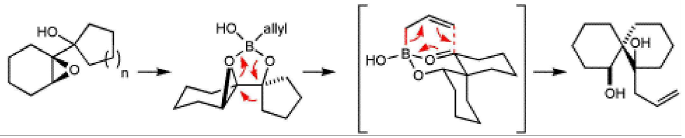
### Problem 909

Contributer: **Christian Markert**
Citation: *Angew. Chem.* **2004**, *43*, 1702

Tu *et al.* reported the following useful construcion that could be used for a diastereoselective generation of the illustrated bicyclic structures with quarternary stereocenters. (*ACIEE* **2004**, *43*, 1702).



Please predict stereochemistry of the product and provide a mechanism that would support your predictions.



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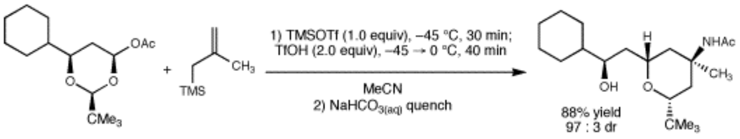
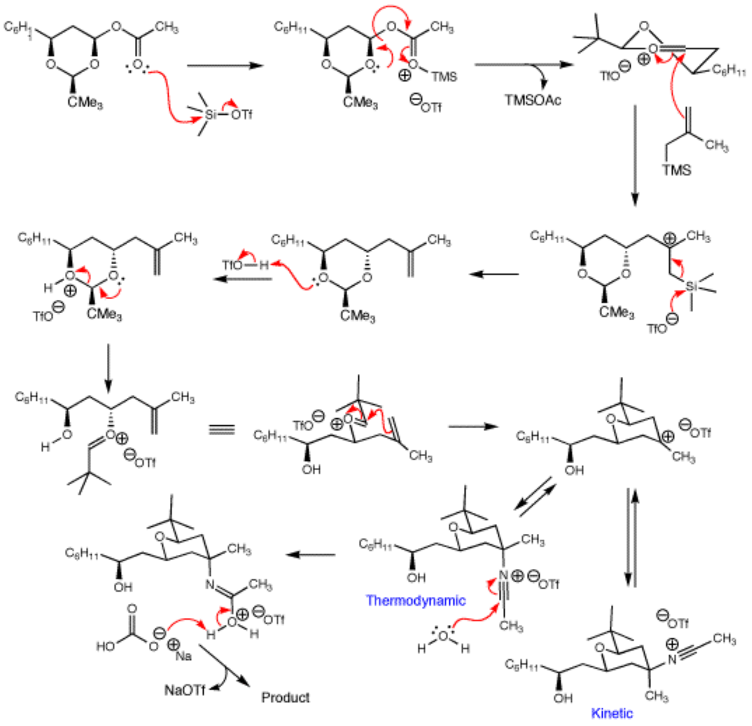
## Problem Answers

### Problem 913

Contributer: **Mathieu Lalonde**
Citation: *J. Am. Chem. Soc.* **2006**, *ASAP*,

The transformation depicted below was recently reported by Rovis and coworkers (Epstein, O. L.; Rovis, T. *J. Am. Chem. Soc.* **2006**, ASAP). Provide a mechanism for this transformation that accounts for the observed diastereoselectivity.


OAc
CMe$_3$
TMS
CH$_3$
1) TMSOTf (1.0 equiv), –45 °C, 30 min; TfOH (2.0 equiv), –45 → 0 °C, 40 min
MeCN
2) NaHCO$_{3(aq)}$ quench
H
NHAc
CH$_3$
OH
88% yield
97 : 3 dr
CMe$_3$



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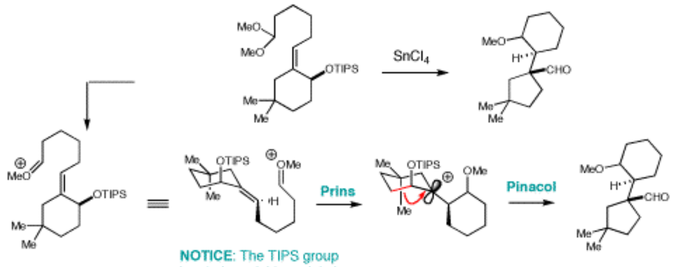
## Problem Answers

### Problem 915

Contributer: **Karl Scheidt**
Citation: *J. Org. Chem.* **2006**, *71*, 1581-1587

Overman has been a major contributor in the field of carbocation chemistry. In 2006, he observed that the following reaction proceeded with complete retention of absolute configuration (*J. Org. Chem.* **2006**, *71*, 1581-1587). Please provide a mechanism for this transformation which includes 3-dimensional structures and a rationale for the stereochemical outcome. Be sure to label all pericyclic processes.



NOTICE: The TIPS group has to be axial too minimize $A_{1,3}$ strain in the system

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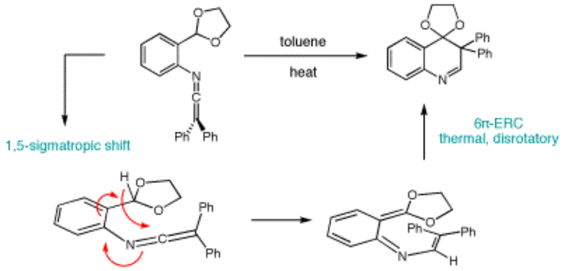
## Problem Answers

## Problem 918

Contributer: **Karl Scheidt**
Citation: *Organic Lett.* **2006**, *81*, 5645-5648

Alajarin and co-workers (*Org. Lett.* **2006**, *8*, 5645-5648) discovered when the following ketenimine is heated in toluene, a cyclization occurs. Please provide a detailed mechanism for this transformation. Be sure to label all pericyclic processes.



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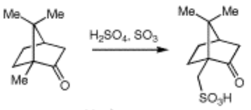
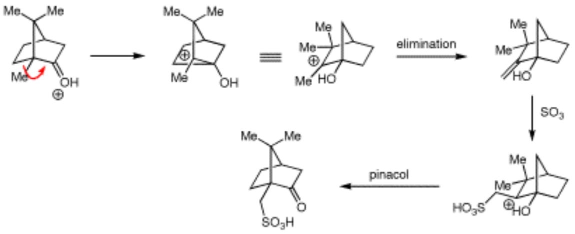
## Problem Answers

### Problem 922

Contributer: **Karl Scheidt**
Citation:

Camphor is prone to rearrangement when exposed to acid. Camphorsulfonic acid (CSA), which is a common reagent in organic synthesis, is formed when camphor is treated sulfuric acid and sulfur trioxide. Please provide a mechanism using 3-dimensional structures.





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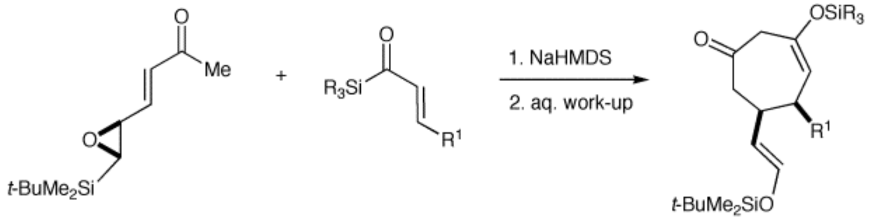
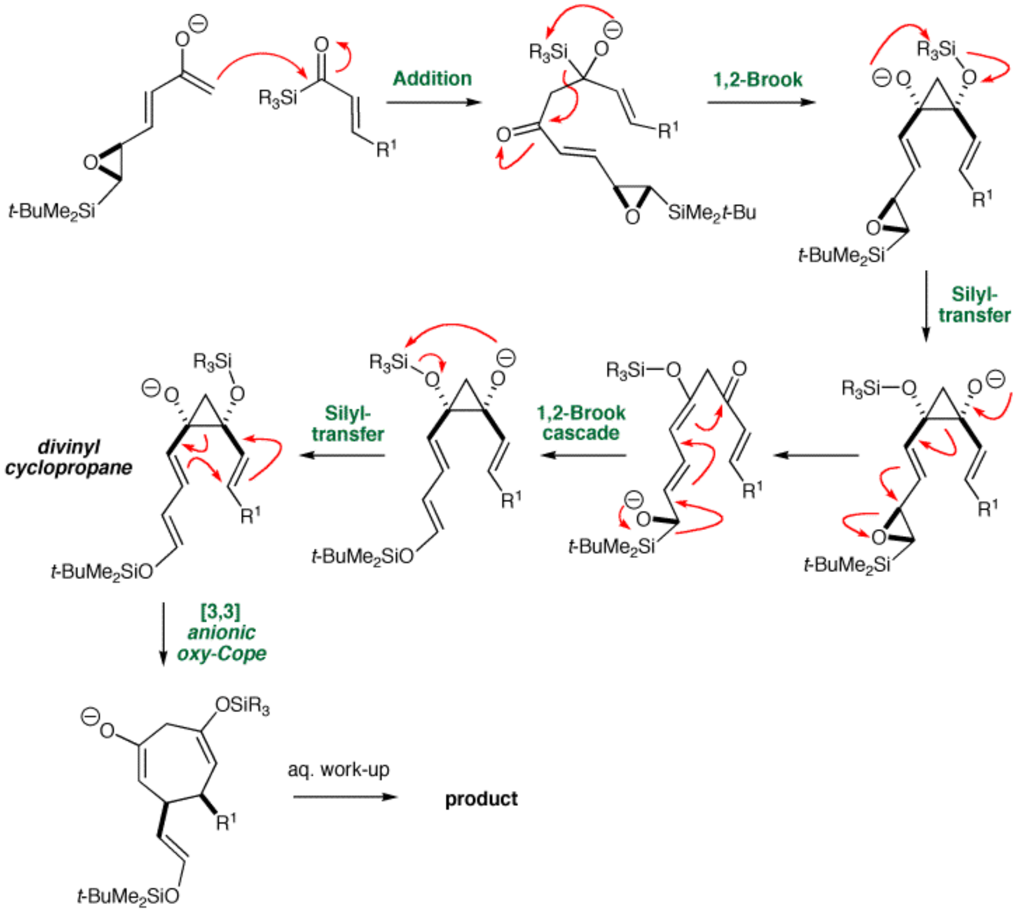
## Problem Answers

### Problem 923

Contributer: **Karl Scheidt**
Citation: *J. Org. Chem.* **2007**, *72*, 1379

Takeda and coworkers recently reported the following formal [3+4] addition for the synthesis of 7-membered ketones (*J. Org. Chem.* **2007**, *72*, 1379). Please provide a mechansim for the generation of the product.





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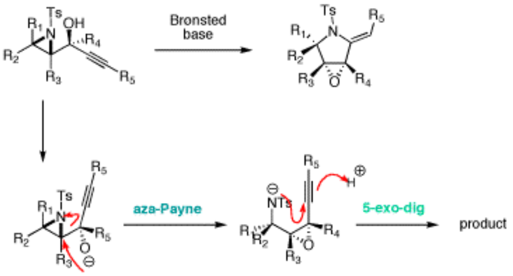
# Problem Answers

## Problem 926

Contributer: **Karl Scheidt**
Citation: *J. Am. Chem. Soc.* **2007**, *129*, 3794

Generally, transition metal catalysis is used for the addition of an N–H group across a pi system (hydroamination). However, Borhan from Michigan State very recently reported a method to perform this reaction with no metal using a Brønsted base (*JACS*, **2007**, *129*, 3794-3795). Please provide a mechanism for this reaction.



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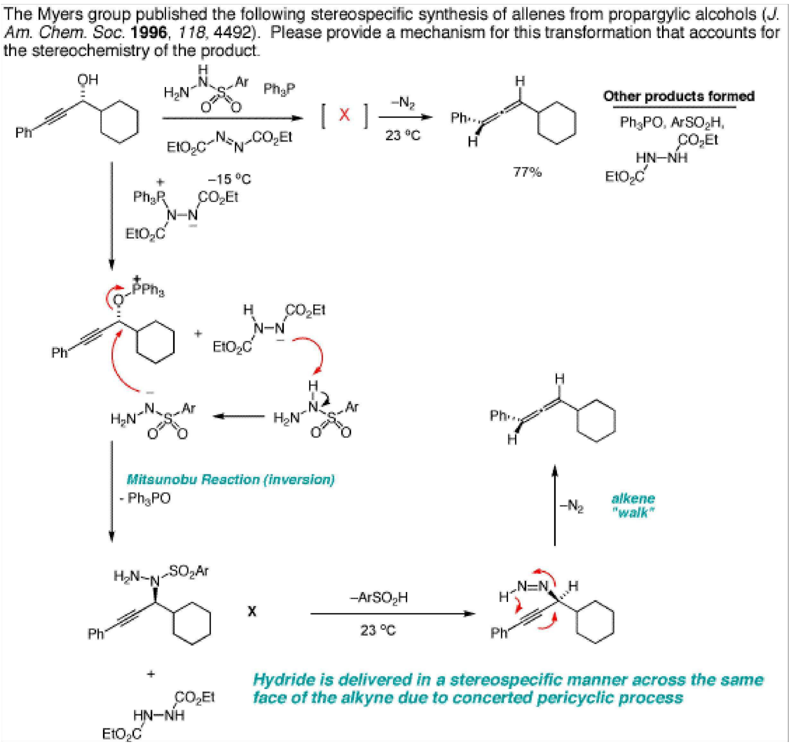
## Problem Answers

### Problem 931

Contributer: **Karl Scheidt**
Citation: *J. Am. Chem. Soc.* **1996**, *118*, 4492



The Myers group published the following stereospecific synthesis of allenes from propargylic alcohols (*J. Am. Chem. Soc.* **1996**, *118*, 4492). Please provide a mechanism for this transformation that accounts for the stereochemistry of the product.

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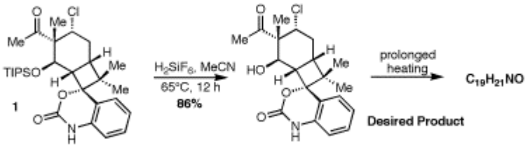
## Problem Answers

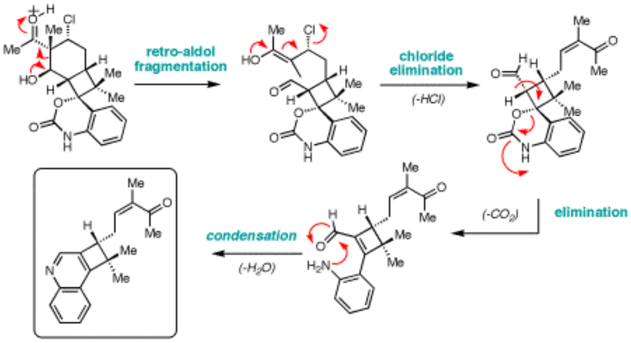
### Problem 932

Contributer: **Thomas Maimone**
Citation:

During their studies directed toward the total synthesis of welwitindolinone A, the Wood group observed the formation of an unusual aromatic heterocycle ($C_{19}H_{21}NO$) after removing the silyl protecting group of **1** (Sarah Reisman thesis, *Yale Univ. 2006*).



Propose a structure for the unknown heterocycle as well as a mechanism for its formation.



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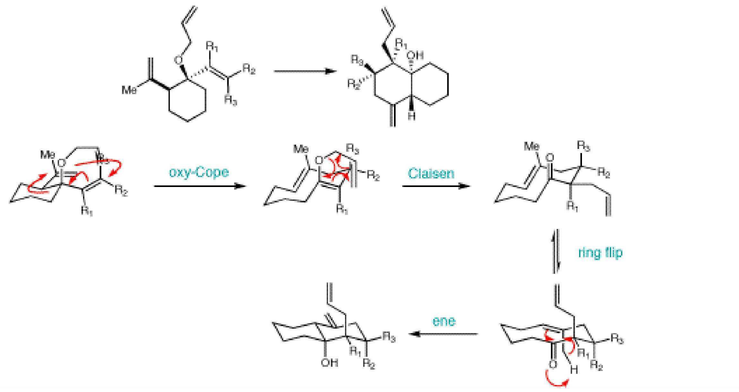
## Problem Answers

### Problem 933

**Contributer:** **Karl Scheidt**
Citation: *J. Am. Chem. Soc.* **2007**, *129*, 2112-2119

Louis Barriault is well known for orchestrating cascade reactions Here is an example from a recent paper (*J. Am. Chem. Soc.* **2007**, *129, 2112-2119).* Please provide a mechanism with 3-dimensional structures.



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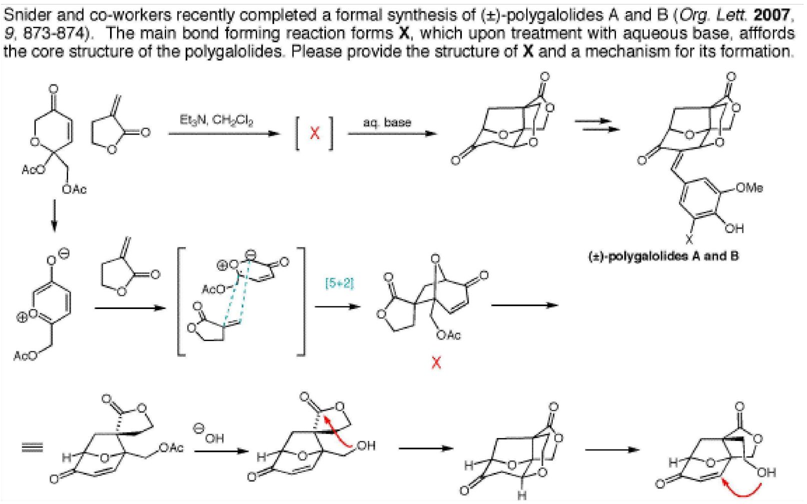
## Problem Answers

**Problem 936** Contributer: **Karl Scheidt**
Citation: *Organic Lett.* **2007**, *9*, 873-874



Snider and co-workers recently completed a formal synthesis of (±)-polygalolides A and B (*Org. Lett.* **2007**, *9*, 873-874). The main bond forming reaction forms **X**, which upon treatment with aqueous base, afffords the core structure of the polygalolides. Please provide the structure of **X** and a mechanism for its formation.

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Department of Chemistry and Chemical Biology, Harvard University

Challenging Problems in Chemistry and Chemical Biology

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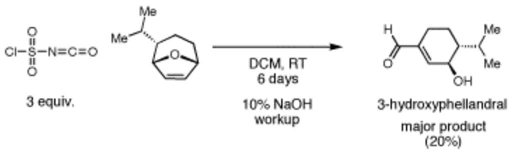
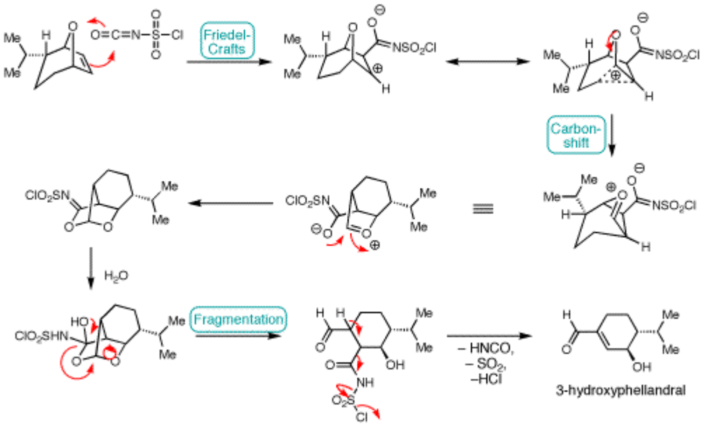
## Problem Answers

### Problem 939

Contributer: **Paul Krawczuk**
Citation: *J. Chem. Soc. Perkin Trans 1* **1993**, 585-587

While working on oxa-analouges of the plant growth-promoting agent helminthosporal, Barbosa and coworkers encountered an unexpected rearangement when they treated the bicyclic alkene below with chlorosulfonyl isocyanate (CSI) (*J. Chem. Soc. Perkin Trans.* 1 **1993** 585-587).





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Department of Chemistry and Chemical Biology, Harvard University

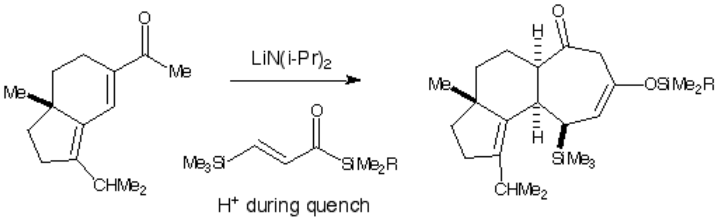
Challenging Problems in Chemistry and Chemical Biology

# Advanced Organic Chemistry Cumulative Exams, Chem 206

## Problem 10

Contributer: **David A.抗 Evans**
Citation: *Organic Lett.* **2000**, *2*, 1903
Keywords: Addition

Takeda and co-workers have recently reported the mechanistically interesting ring extension reaction illustrated below (*Org. Lett.* **2000**, 2, 1903).

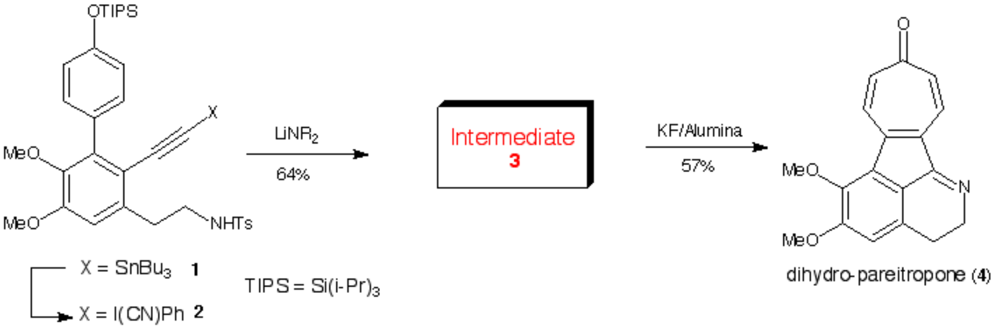


Provide a plausible mechanism for this transformation in the space below.
*Ignore the stereochemical aspect of this transformation.*

## Problem 12

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2002**, *124*, 11600
Keywords: Addition

An elegant synthesis of pareitropone (**5**) was recently reported by Feldman (*J. Am. Chem. Soc* **2002**, *124*, 11600). The first reaction was staged by the generation of the iodoacetylide **2** which was treated with $LiNR_2$ without purification to form intermediate **3** which was immediately transformed into the dihydro-pareitropone (**4**) in with KF and alumina. The synthesis of **5** was completed by air oxidation of **4**.

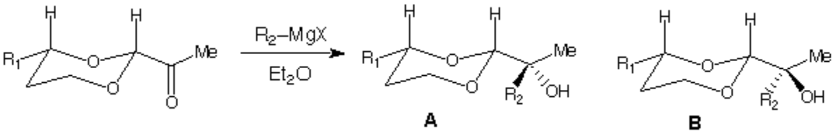


Provide a plausible mechanism for the conversion of **2** to **4** and identify the structure of **intermediate 3**.

## Problem 14

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2001**, *3*, 1865
Keywords: Addition

The following carbonyl addition reactions were recently reported by Bailey (*Org. Lett.* **2001**, 3, 1865-1868). Rationalize the origin of reaction diastereoselelctivity for this addition process.



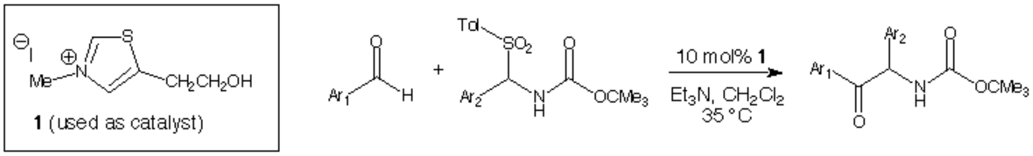
| | $R_2$–MgX | A:B ratio |
|---|---|---|
| $R_1$ = Me | $R_2$ = Ph | 93:7 |
| $R_1$ = $CMe_3$ | $R_2$ = Me | 91:9 |

Provide your answer in the space below:

### Problem 16

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2001**, *123*, 9696
Keywords: Addition

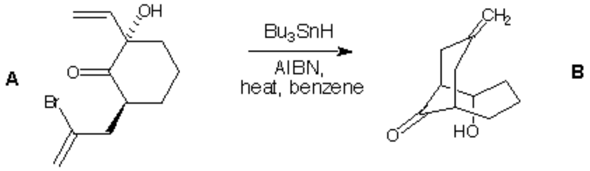
The reaction illustrated below was recently reported by Murry and co-workers from the Merck Process Group (*JACS* **2001**, *123*, 9696-9697). Provide a mechanism for this transformation in the space below.



### Problem 18

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2001**, *3*, 1181-1183
Keywords: Addition

The following transformation was recently reported by Rodriguez (*Org. Lett.* **2001**, *3*, 1181-1183).



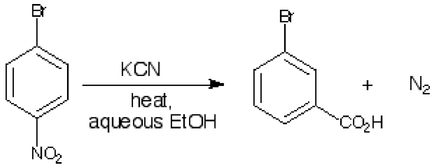
**Part A** What is the structure and function of AIBN in this reaction?

**Part B** Provide a mechanism for the illustrated rearrangement(s) of **A** to **B.** Where stereochemical issues are present, provide clear three dimensional drawings to support your answer.

### Problem 21

Contributer: **David A. Evans**
Citation:
Keywords: Addition

The **Von Richter** reaction is illustrated in the accompanying equation. Please provide a plausible mechanism for this transformation taking into account the following observations. (a) If $^{15}$N-labeled KCN is used, the N$_2$ formed is half labeled; (b) 3-bromo-benzonitrile does not form 3-bromo-benzoic acid under the reaction conditions.

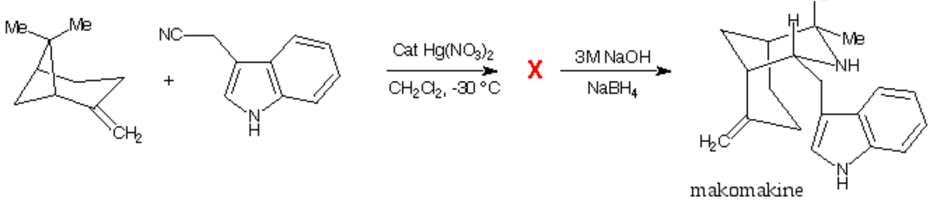


Provide your answer in the space below:

### Problem 22

Contributer: **David A. Evans**
Citation: *Chem. Commun.* **1983**, 384
Keywords: Addition

An interesting example of the **Ritter Reaction** was reported some time ago by R. V. Stevens (*Chem. Comm.* 384 **1983**). The relevant process illustrated below afforded an efficient two-step synthesis of makomakine. In contemplating this transformation, view Hg(2+), to be functioning as a catalyst in the production of **X**.



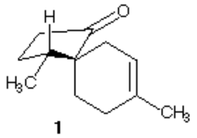
makomakine

In the space below, provide a mechanism for the illustrated two-step transformation and identify the structure **X**.

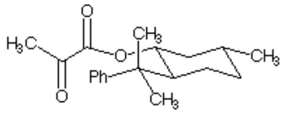
### Problem 24

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2000**, *122*, 9556
Keywords: Addition

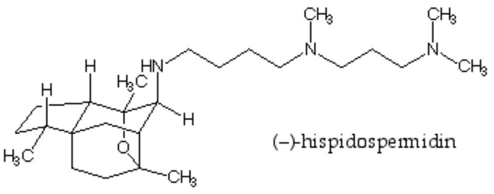
Sorensen and coworkers recently reported the synthesis of (–)-hispidospermidin (Sorensen *J. Am. Chem. Soc.* **2000**, *122*, 9556). The **Shapiro Reaction**, along with methodology developed by Whitesell, was use in the construction of intermediate **3** from the indicated building blocks **1** and **2** (eq 1).



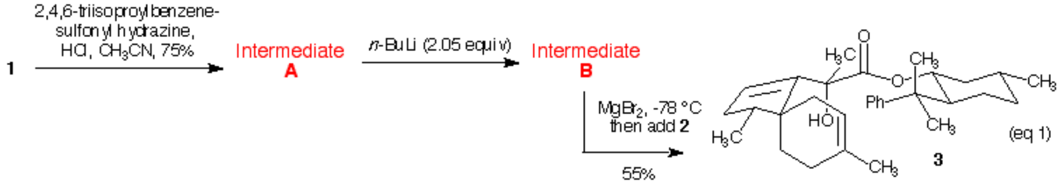
**1**



**2**



(–)-hispidospermidin



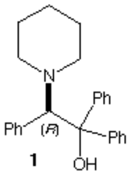
**Part A.** Provide a mechanism for the **Shapiro Reaction** of **1** to intermediate **B** in the space below. Feel free to use a simplified analog of **1** such as 2,2-dimethylcyclopentanone to answer this question.

**Part B.** Provide a mechanism for the **transformation** of intermediate **B** to the illustrated product **3.** Use 3-dimensional representations to illustrate the stereochemical aspects of this individual step.

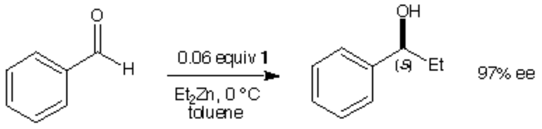
## Problem 27

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2000**, *65*, 7303
Keywords: Addition

Chiral amino alcohol **1** efficiently mediates the addition of diethylzinc to aromatic aldehydes. While a number of other amino alcohols are also effective in controlling the absolute course of the addition process, this amino alcohol has been the focus of a recent computational investigation that addresses the preferred transition state geometry for this addition process (Pericas, et al. *J. Org. Chem.* **2000**, *65*, 7303 and references cited therein). It should be noted that, while **1** is not the actual catalyst, it is modified under the reaction conditions to the competent catalytic agent.



**1**

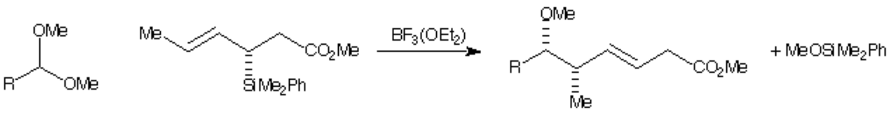


Provide a detailed mechanism for the overall transformation in the space below. Use three-dimensional representations to illustrate the absolute stereochemical aspects of the indicated transformation.

## Problem 29

Contributer: **David A. Evans**
Citation: *Chem. Rev.* **1995**, *95*, 1293-1316
Keywords: Addition

In his seminar at Harvard on April 17, 2000, Professor Panek described a number of diastereoselective transformations based on chiral allylsilanes. One such transformation is provided below.



*syn/anti diastereoselection 2–40:1*

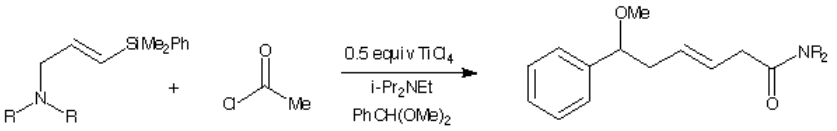
**Part A.** Provide a detailed mechanism for the illustrated transformation in the space below. Use three-dimensional representations, where relevant, illustrate the stereochemical aspects of the individual steps.

**Part B.** In principle, both *syn* and *anti* product diastereomers are possible. In the space below, rationalize the preference for *syn* reaction diastereoselection from both allylsilane geometries. Use antiperiplanar transition states.

## Problem 31

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1999**, *121*, 9726
Keywords: Addition

In the Panek lecture he described the transformation illustrated below. This transformation is an extrapolation of the recent publication of MacMillan and co-workers (*JACS*, **1999**, *121*, 9726).

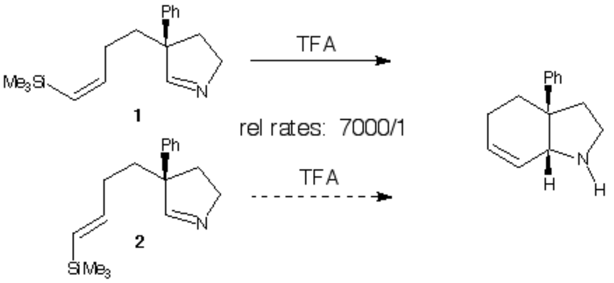


Provide a detailed mechanism for the illustrated transformation. Use three-dimensional representations, where relevant, to illustrate the stereochemical aspects of the individual steps.

## Problem 32

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1984**, *25*, 5739
Keywords: Addition

Overman carried out the cyclizations of the illustrated (E) and (Z) vinylsilanes **1** and **2**, both of which afforded the indicated product (Overman et al. *TL* **1984**, *25*, 5739). He observed that **1** cyclizes 7000-times faster than **2**.



Overman et al. *TL* **1984**, *25*, 5739.

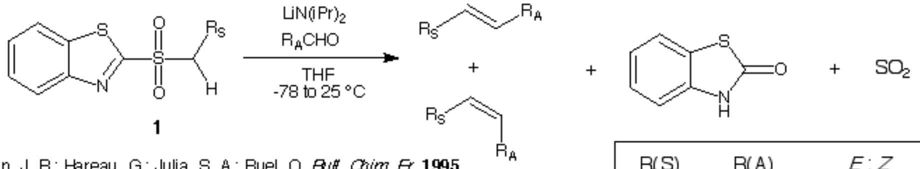
**Part A.** Provide a detailed mechanism for the transformation of **1** and **2** to the illustrated product. Use three-dimensional representations, where relevant, to illustrate your answer.

**Part B.** In addition, rationalize the illustrated rate difference for the individual cyclizations.

## Problem 37

Contributer: **David A. Evans**
Citation: *Synthesis* **1996**, 285
Keywords: Addition

The stereoselective construction of trans olefins through carbanion-mediated condensation processes has still not been rendered general. One transformation that may be used in certain circumstances is the "one-step" Julia transformation illustrated below:



Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Bull. Chim. Fr.* **1995**, 856; *ibid*, **1993**, *130*, 336; *ibid*, *Tetrahedron Lett.* **1991**, *32*, 1175. A synthetic application: Kocienski *Synthesis* **1996**, 285.

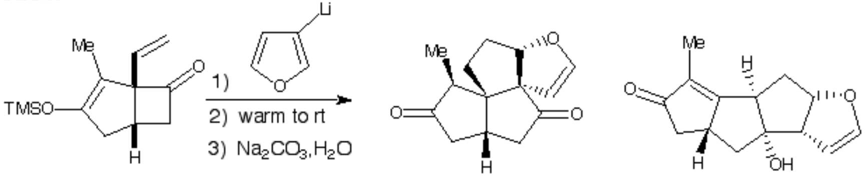
| R(S) | R(A) | *E* : *Z* | yield |
|---|---|---|---|
| Ph | *n*-octyl | 23 : 77 | 80 % |
| Ph | cyclohexane | 60 : 40 | 67 % |
| Ph | *tert*-butyl | 99 : 01 | 63 % |
| Ph | cyclohexene | 99 : 01 | 71 % |
| *n*-Pr | *p*-MeO-Ph | 99 : 01 | 95 % |
| *n*-Pr | Ph | 94 : 06 | 68 % |
| *n*-Pr | *p*-Cl-Ph | 77 : 23 | 51 % |

In the space below, draw out each of the intermediates that might be anticipated in the transformation of **1** to the olefinic products. Since the purpose of this question is to test your knowledge of the probable intermediates, you may ignore the stereochemical implications of this question. In fact, the stereochemical details of this process have not yet been revealed.

## Problem 43

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1996**, *61*, 7976
Keywords: Addition

Moore (*J. Org. Chem.* **1996**, *61*, 7976) recently reported the elegant 3-step transformation that is illustrated by the specific example below.



**1**, major (57%) **2**, minor (11%)

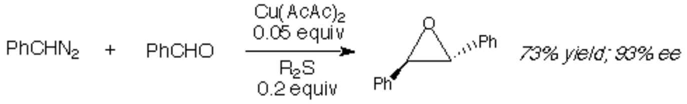
**Part A.** Draw out a plausible mechanism for the transformation to the major product isomer **1**.

**Part B.** Draw out a plausible mechanism for the transformation to the minor product isomer **2**.

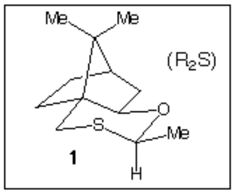
## Problem 44

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1996**, *118*, 7004
Keywords: Addition

Aggarwal (*J. Am. Chem. Soc.* **1996**, *118*, 7004) recently reported the enantioselective aldehyde epoxidation illustrated below. One of the important issues to be addressed in this question is how **1**, used in sub-stoichiometric quantities, is capable of controling the absolute stereochemical outcome of the process. *The absolute configurations of both* **1** *and stilbene oxide are as illustrated.* Provide answers to the two questions pertaining to this transformation posed below and on the following page.



*73% yield; 93% ee*



**1**

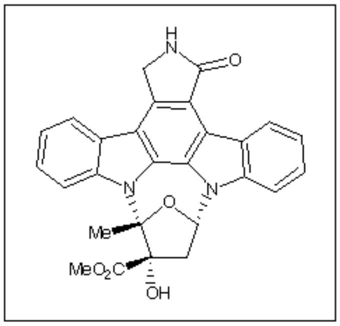
**Part A.** Draw out each of the steps in this transformation. Since you are not asked to address the stereochemical aspects of the reaction here, **1** may be simplified as $R_2S$. At the bottom of the page draw out the catalytic cycle.

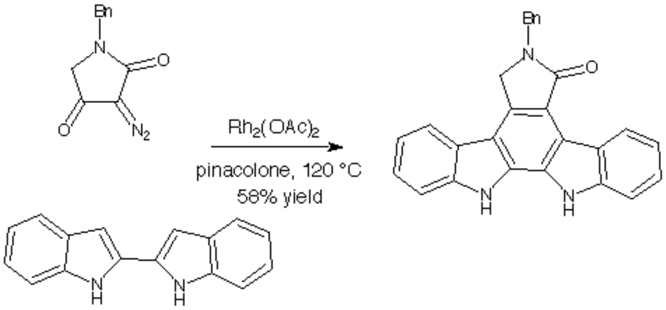
**Part B .** Clearly explain how **1** imparts chirality to the epoxidation process. Your answer should clearly explain the absolute stereochemical outcome of the process.

## Problem 47

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1995**, *117*, 10413
Keywords: Addition

Wood recently reported a very clever approach to the synthesis of the indolocarbazole family of natural products (*JACS* **1995**, *117*, 10413). His approach to the indolocarbazole core is the one-pot transformation outlined below.



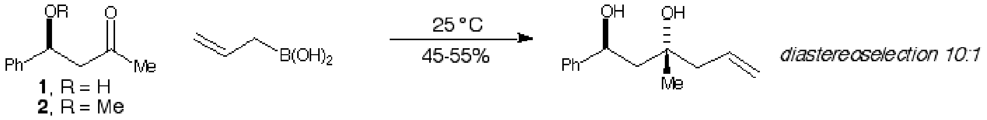


Provide a plausible mechanism for this multi-step transformation in the space below.

## Problem 48

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1996**, *37*, 2181
Keywords: Addition

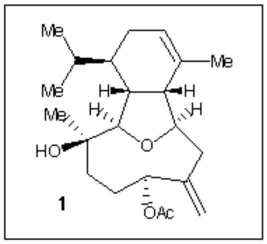
The following transformation was recently reported by Kabalka (*Tetrahedron Lett.* **1996**, *37*, 2181). Treatment of **1** with allylboronic acid afforded the indicated adduct in high yield with 10:1 diastereoselection. On the other hand, the analogous reaction of **2** was nonstereoselective. Propose a mechanism for this transformation that accounts for the stereochemical outcome of the addition process.

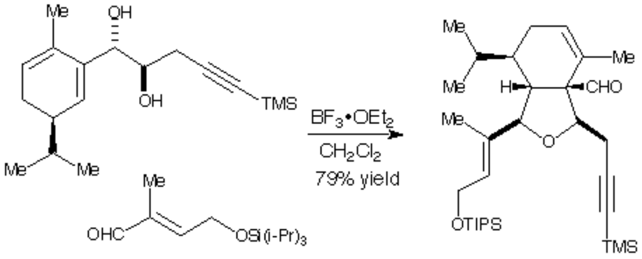


## Problem 49

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1995**, *117*, 10391
Keywords: Addition

Overman and MacMillan (*JACS* **1995**, *117*, 10391) recently reported the synthesis of the diterpene, 7-deacetoxyalcyonin (**1**) illustrated below. The keynote reaction in this synthesis is the Lewis acid catalyzed transformation illustrated below, a process that has previously been investigated in the Overman Group (*JACS* **1991**, *113*, 3534).



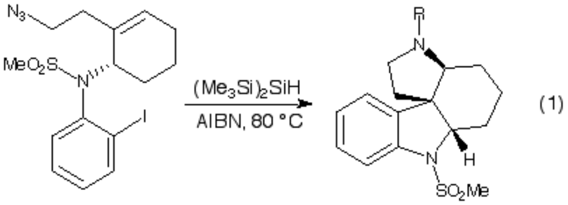


Propose a detailed mechanism for this transformation. Be sure to clearly identify the stereochemical control elements that are operating in the creation of the new stereogenic centers.

## Problem 50

Contributer: **David A. Evans**
Citation: *Chem. Commun.* **1995**, 1409
Keywords: Addition

Murphy (*Chem. Comm.* **1995**, 1409) recently reported a very efficient approach to the synthesis of the aspidosperma alkaloid skeleton (eq 1).

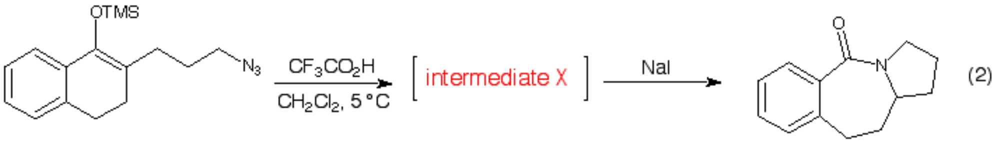


Provide a plausible mechanism for this transformation in the space provided below.

## Problem 51

Contributer: **David A. Evans**
Citation: *Tetrahedron* **1996**, *52*, 3403
Keywords: Addition

Aube (*Tetrahedron* **1996**, 52, 3403) recently reported an efficient approach to the synthesis of polycyclic lactams. A typical transformation is provided below (eq 2).

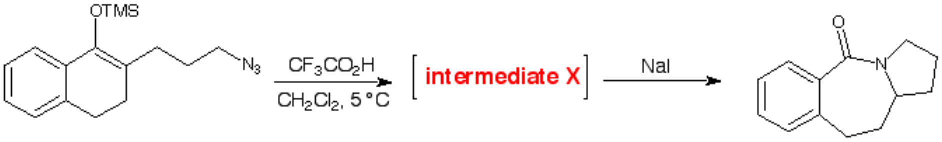


Provide a plausible mechanism for this transformation in the space below.

## Problem 54

Contributer: **David A. Evans**
Citation: *Tetrahedron* **1996**, *52*, 3403
Keywords: Addition

Aube (*Tetrahedron* **1996**, 52, 3403) recently reported an efficient approach to the synthesis of polycyclic lactams. A typical transformation is provided below.

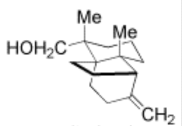


Provide a plausible mechanism for this transformation in the space below.

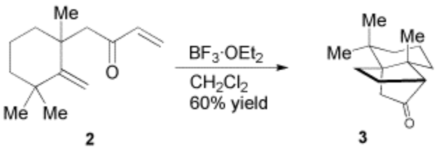
## Problem 56

Contributer: **Grace Wang**
Citation: *Chem. Commun.* **1994**, 2259
Keywords: Addition

The recently isolated irregular sesquiterpene myltaylenol (**1**) stimulated Srikrishna and co-workers (*Chem. Commun.* **1994**, 2259) to study the biogenetically modeled acid-promoted rearrangement of **2** which leads to the desired terpenoid skeleton in good yield. In the space below, provide a detailed mechanism for the transformation of **2** to **3**.



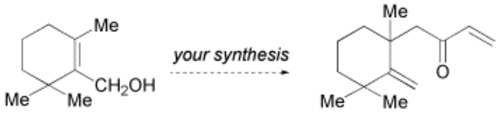
myltaylenol
**1**



**2** **3**

A.Srikrishna, *Chem. Commun.* **1994**, 2259.

Provide an expedient synthesis of **2** from the allylic alcohol **4**.

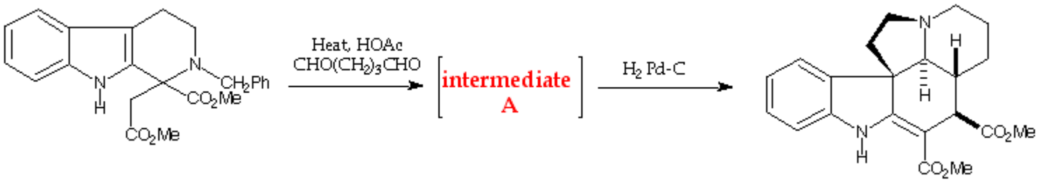


**4** **2**

## Problem 60

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1987**, *28*, 1267
Keywords: Addition

Provide a detailed mechanism for the cyclization reported by Vercautern and co-workers (*Tetrahedron Lett.* **1987**, *28*, 1267).

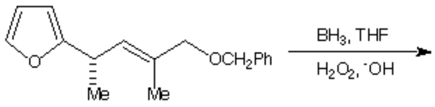


**Your mechanism for this transformation**

## Problem 61

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1979**, *101*, 259
Keywords: Addition

The following stereoselective hydroboration has been reported by Kishi in his synthesis of monensin (*JACS* **1979**, *101*, 259).
Provide the stereostructure of the major product and rationalize the stereochemical outcome as indicated in the directions.



The product ?
*Stereoselection: 8/1*

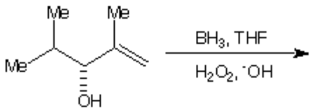
*product structure*

**The rationalization ?**

## Problem 62

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1983**, *105*, 2487
Keywords: Addition

The following stereoselective hydroboration has been reported by Still ( *JACS* **1983**, *105*, 2487).
Provide the stereostructure of the major product and rationalize the stereochemical outcome as indicated in the directions.



The product ?
*Stereoselection: 24/1*

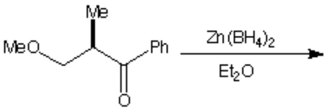
*product structure*

**The rationalization ?**

## Problem 63

Contributer: **David A. Evans**
Citation: *Chem. Pharm. Bull. Japan* **1984**, *32*, 1411
Keywords: Addition

The following stereoselective reduction has been reported by Oishi (*Chem. Pharm. Bull.* **1984**, *32*, 1411).
Provide the stereostructure of the major product and rationalize the stereochemical outcome as indicated in the directions.



The product ?
*Stereoselection: 32/1*

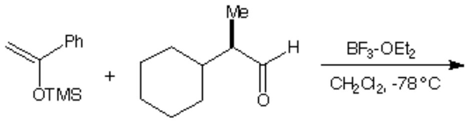
*product structure*

**The rationalization ?**

## Problem 64

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1983**, *105*, 1667
Keywords: Addition

The following stereoselective aldol addition reaction has been reported by Heathcock (*J. Am. Chem. Soc.* **1983**, *105*, 1667).
Provide the stereostructure of the major product and rationalize the stereochemical outcome as indicated in the directions.



The product ?
*Stereoselection: 16/1*

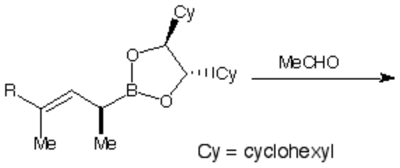
*product structure*

**The rationalization ?**

## Problem 66

Contributer: **David A. Evans**
Citation: *Liebig's Ann. Chem.* **1991**, 1203
Keywords: Addition

The following stereoselective transformation has been reported by Hoffmann (*Liebig's Ann. Chem.* **1991**, 1203).
Provide the stereostructure of the major product and rationalize the stereochemical outcome as indicated in the directions.



The product ?
*Stereoselection: >20:1*

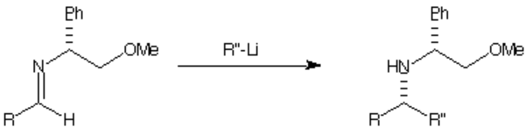
*product structure*

**The rationalization ?**

## Problem 69

Contributer: **David A. Evans**
Citation: *Chem. Lett.* **1991**, 1555
Keywords: Addition

The following stereoselective transformation has been reported by Fujisawa (*Chem.Lett.* **1991**, 1555). Given the stereostructure of the product, rationalize the stereochemical outcome.



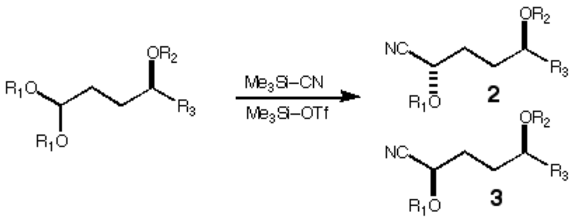
stereoselection >97:3

**The rationalization ?**

## Problem 71

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1991**, 3608
Keywords: Addition

The development of stereocontrolled reactions is an important undertaking in organic synthesis. Recently, Molander and Haar disclosed "A Simple Method for Achieving High 1,4-Relative Asymmetric Induction in Carbonyl Reactions" (*JACS* **1991**, *13*, 3608). Their reaction is show below (eq 1).



| $R_1$- | $R_2$- | $R_3$- | Ratio, **2** : **3** |
|---|---|---|---|
| Me- | Me- | Me- | 1.5 : 1 |
| *i*-Pr- | Me- | Me- | 5 : 1 |
| *i*-Pr- | Me- | *i*-Pr- | 15 : 1 |

**Conditions**: 10 mol % Trimethylsilyl triflate with 1 equiv each of TMSCN and acetal, -78 °C in $CH_2Cl_2$.

**Part A** (10 points). Write out a detailed mechanism for the illustrated transformation. *I am not interested in the stereochemical details yet*; rather, I am interested in seeing whether you can write out the key activation steps and intermediates in the process. Speculate on the rate-determining step.

**Part B** (10 points). Provide a detailed rationale for the stereochemical aspects of the process. Your answer should include carefully rendered *perspective drawings* illustrating the preferred conformations of relevant intermediates. Your answer should also include an explanation of the observed variation in reaction diastereoselection with substrate variables $R_1$, $R_2$, and $R_3$.

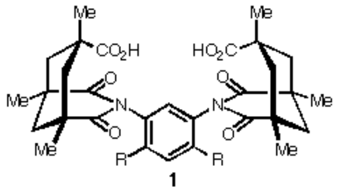
**Part C** (10 points). Molander suggests that the concepts revealed in this transformation might be extended to other reaction types. This being the case, what other reactions do you perceive might also exhibit the same stereochemical attributes? For full credit on this part, I want you to provide two different examples.

## Problem 74

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1988**, *110*, 5192
Keywords: Addition

Over the last several years Rebek and co-workers have published a series of papers on a new class of chelating ligands, or "molecular clefts," such as the one illustrated below ,[*J. Am. Chem. Soc.* **110**, 5192 (1988), and papers cited therein]. In this recent paper, the exceptional binding affinity for divalent ions is demonstrated. For example, **1** (R = Me) exhibits a binding affinity for $Ca^{+2}$ of ca. $10^{+5}$.

**A.** Discuss the unique design features of this chelating agent which render it so effective in chelation. Include in your discussion why the derivative, R = Me was chosen over the simpler analog, R = H.



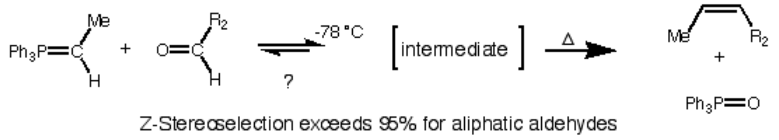
1

**B.** Rebek has cleverly chosen his system so that he can increase the distance between the carboxyl ligands without losing the organizational features of his "cleft". Show how you might synthesize an analog, having comparable organizational constraints, but with an *increased* distance between ligating functionality. What types of substrates do you anticipate might bind to your new ligand. A nice review of this work has recently appeared in *Science*, **235**, 1478-1484 (1987).

## Problem 77

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1988**, *110*, 3948
Keywords: Addition

The Wittig reaction (and its numerous variants) continues to be one of the most powerful reactions for the stereoselective construction of olefins. By virtue of its importance in synthesis, the mechanism of this reaction has been intensely studied by a number of individuals, and a continuing evolution of thought, backed by experimental data, on the projected mechanism of this reaction is still in progress. A recent paper by Vedejs and co-workers [ *J. Am. Chem. Soc.* **110**, 3948 (1988)], provides an excellent overview on the current thinking on the mechanism of the "salt-free" Wittig Reaction which proceeds with high levels of Z-olefin selectivity with monosubstituted triphenylphosporanes . Having read this important paper, answer the questions posed below.



Z-Stereoselection exceeds 95% for aliphatic aldehydes

**A.** What is meant by a "salt-free" Wittig reaction ? Describe precisely how you would carry out such a reaction.

**B.** What is the initial *observable* intermediate in this reaction at low temperatures? Draw its structure. If more than one intermediate is possible, draw its structure as well and rank them in order of stability.

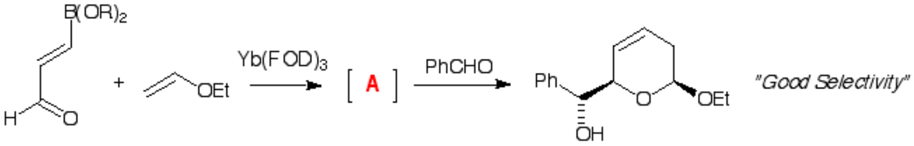
**C.** What is the product-determining step in the reaction? Is it the same as the rate-determining step? Clearly identify which steps are reversible and which steps are not.

**D.** Rationalize, via Newman Projections and associated discussion, the high cis-olefin selectivity for the salt-free Wittig process. Identify the nonbonding interactions identified in the Vedejs model which dictate stereocontrol.

## Problem 78

Contributer: **David A. Evans**
Citation: *Chem. Commun.* **2003**, 276
Keywords: Addition

The illustrated diastereoselective dihydropyran synthesis has been reported by Deligny and co-workers (*Chem Commun.* **2003**, 276).



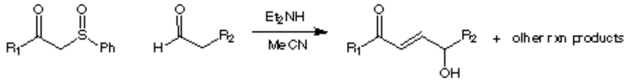
*"Good Selectivity"*

Provide a plausible mechanism for this reaction sequence. Your answer should include three-dimensional structures that accurately depict ground and transition state representations.

## Problem 83

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2001**, *66*, 1228
Keywords: Addition

The illustrated Knovenagel-type condensation recently reported by Nokami et al. (*J. Org. Chem.* 2001, *66*, 1228) should prove to be a generally useful transformation.

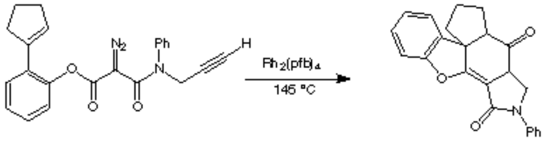


In the space below, provide a mechanism for the indicated transformation.

## Problem 89

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2001**, *ASAP*,
Keywords: Addition

Padwa and co-workers recently disclosed the illustrated multistep polycyclisation as a possible route to the strychnine core ( *Org. Lett.* 2001, ASAP)

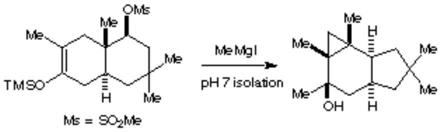


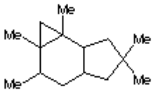
In the space below, provide a mechanism for the indicated transformation. *Hint: The management suggests that a carefull bidirectional analysis might help you to arrive at a sollution of this question.*

## Problem 90

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2001**, *66*, 2350
Keywords: Addition

The synthesis of the marasmane sesquiterpene skeleton has been to topic of several research groups. In a recent paper (*J. Org. Chem.* 2001, *66*, 2350) de Groot et al. have developed an ingeneous approach to the assemblage of this ring system.





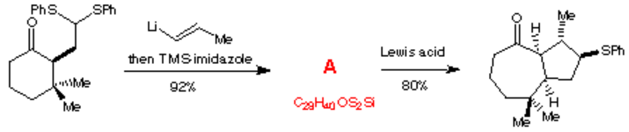
marasmane skeleton

In the space below, provide a mechanism for the indicated transformation.

## Problem 92

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2001**, *123*, 4851
Keywords: Addition

In Overman's synthesis of shahamin K (*J. Am. Chem. Soc.* 2001, *123*, 4851), the key transformtion involves the interesting reaction sequence shown below.



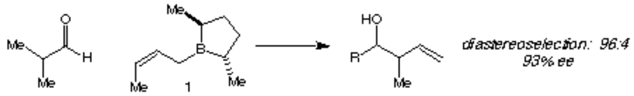
major diastereomer

Please provide a mechanism for this two-step process and identify intermediate A.

## Problem 93

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1987**, *52*, 4831
Keywords: Addition

S. Masamune has reported the illustrated allylboration (*J. Org. Chem.* 1987, *52*, 4831).

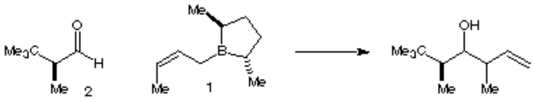


Predict the stereochemical outcome of the reaction and draw the relevant Zimmerman-Traxler transition state!

## Problem 94

Contributer: **David A. Evans**
Citation:
Keywords: Addition

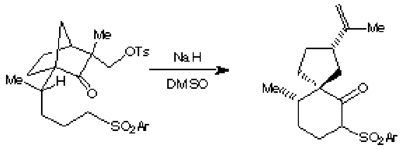
The reaction of 1 with 2 is a typical example of a double stereodifferentiating addition reaction. Determine whether this reaction is "matched" or mismatched, draw the transition state for the addition process that supports your conclusion, and provide the absolute stereochemicry of the addition product.



## Problem 95

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1978**, *43*, 1750
Keywords: Addition

Magnus et al; have reported the base-induced transformation shown below (*J. Org. Chem* 1978, *43*, 1750).

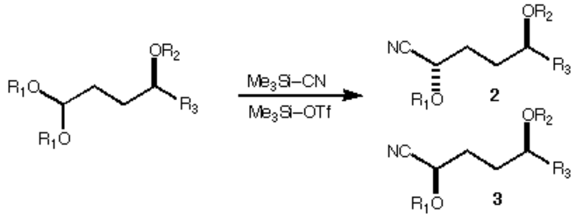


Provide a detailed mechanism for this transformation in the space below.

## Problem 97

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1991**, *113*, 3608
Keywords: Addition

The development of stereocontrolled reactions is an important undertaking in organic synthesis. Molander has disclosed "A Simple Method for Achieving High 1,4-Relative Asymmetric Induction in Carbonyl Reactions" (*JACS* **1991**, *13*, 3608). Their reaction is show below (eq 1).



| $R_1$- | $R_2$- | $R_3$- | Ratio, **2** : **3** |
|---|---|---|---|
| Me- | Me- | Me- | 1.5 : 1 |
| *i*-Pr- | Me- | Me- | 5 : 1 |
| *i*-Pr- | Me- | *i*-Pr- | 15 : 1 |

**Conditions**: 10 mol % Trimethylsilyl triflate with 1 equiv each of TMSCN and acetal, -78 °C in $CH_2Cl_2$.

**Part A.** Write out a detailed mechanism for the illustrated transformation. *I am not interested in the stereochemical details yet*; rather, I am interested in seeing whether you can write out the key activation steps and intermediates in the process. Speculate on the rate-determining step.

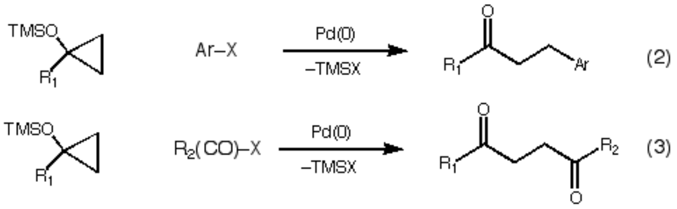
**Part B.** Provide a detailed rationale for the stereochemical aspects of the process. Your answer should include carefully rendered *perspective drawings* illustrating the preferred conformations of relevant intermediates. Your answer should also include an explanation of the observed variation in reaction diastereoselection with substrate variables $R_1$, $R_2$, and $R_3$.

**Part C.** Molander suggests that the concepts revealed in this transformation might be extended to other reaction types. This being the case, what other reactions do you perceive might also exhibit the same stereochemical attributes?

## Problem 98

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1991**, *45*, 2809
Keywords: Addition

Cyclopropanol derivatives are proving to be useful homoenolate anion equivalents, and over the last ten years metal-catalyzed reactions utilizing these intermediates in useful bond constructions have appeared. In 1988 the illustrated arylation reaction was reported, *JACS* **1988**, *110*, 3296, (eq 2) while more recently, Nakamura (*J.Org. Chem.* **1991**, *56*, 2809) reported a thorough study on the related acylation reactions (eq 3).



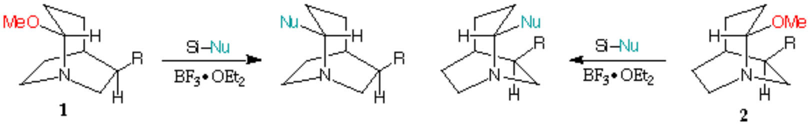
**Part A.** Write out the probable steps, *in equation form*, for the Pd-catalyzed transformation shown in eq 2.

**Part B.** There appear to be some definite requirements for the Ar–X reacting partner in the arylation. For example, these reactions afford excellent yields of the desired product when aryl triflates are employed. On the other hand, aryl iodides fail to provide the desired product. Based on the mechanism which you have provided in Part A, speculate why aryl triflates, but not the analogous iodides, are required for coupling.

## Problem 102

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2002**, *4*, 3179-3182
Keywords: Addition

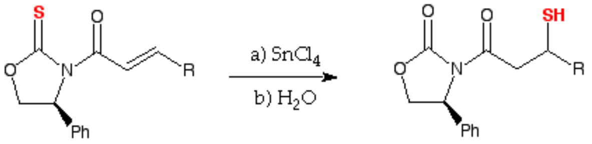
A stereospecific substitution process was recently reported by H. M. R.Hoffmann (*Org. Lett* **2002**, *4*, 3179-3182). Both **1** and **2** undergo stereospecific replacement of the methoxyl substituent upon treatment with a Lewis acid catalyst and a silyl nucleophile (Nu = CN, $N_3$, alkyne, etc). Provide a plausible mechanism for the indicated transformations.



## Problem 103

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **2003**, *44*, 1129-1132
Keywords: Addition

The following intramolecular sulfur transfer process was recently reported by Ortiz (*Tetrahedron Lett.* **2003**, *44*, 1129-1132) and earlier by Palomo (*JACS* **2001**, *123*, 5602). Predict the stereochemical outcome of this transformation.

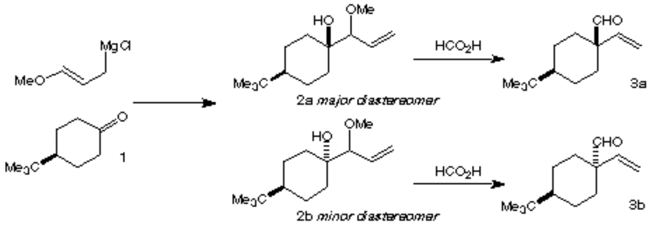


diastereoselection ~98:2 (72%)

## Problem 104

Contributer: **David A. Evans**
Citation: *Evans, Unpublished Results*
Keywords: Addition

The indicated allylmetal nucleophile adds regioselectively to the indicated cyclohexanone derivative 1 to afford the tertiary alcohols 2a and 2b having the indicated stereochemistry (Evans & Andrews, *Unpublished*, 1974). These adducts may be individually rearranged to the indicated aldehydes 3a and 3b with complete control of stereochemistry. This set of transformations readily provides access to functionalized quaternary centers.

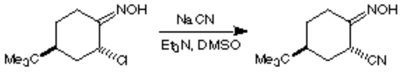


Provide a mechanism for the transformation of 2a into 3a that is consistent with the experimental observations. Where appropriate, provide three-dimensional drawings to reinforce your answer.

## Problem 110

Contributer: **David A. Evans**
Citation:
Keywords: Addition

The indicated transformation occurs with apparent retenton of stereochemistry.

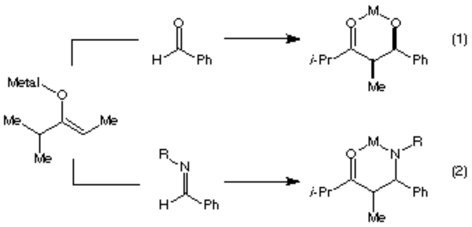


In the space below, provide an explanation for the mechanism and stereochemical outcome of this transformation.

## Problem 111

Contributer: **David A. Evans**
Citation:
Keywords: Addition

The Zimmerman-Traxler transition state nicely correlates starting enolate geometry and product aldol stereochemistry. This point is illustrated in equation 1 below in the correlation of the (Z) enolate geometry with the syn aldol product stereochemistry. The intent of this question is to have you ponder the related addition to the illustrated imine (eq 2).

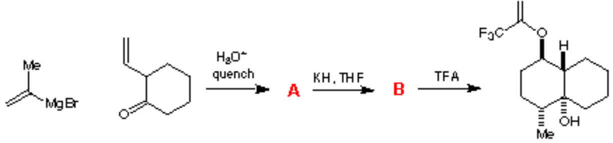


In the space below, draw the Zimmerman-Traxler transition state for the "imine-aldol" process (eq 2) and illustrate the predicted stereochemical outcome of the addition reaction. Assume that the imine geometry cannot isomerize under the reaction conditions.

## Problem 114

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **2001**, *42*, 3816
Keywords: Addition

The following transformation was reported earlier this year by J. D. White and co-workers (*Tet Lett*. 2001, 42, 3816.). From your knowledge of the chemistry involved, provide a mechanism for the indicated transformation which is consistant with the observed product stereochemistry.

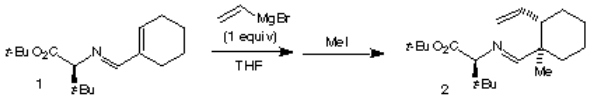


TFA = trifluoroacetic acid

## Problem 115

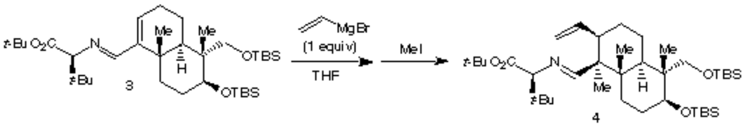
Contributer: **David A. Evans**
Citation: *Organic Lett.* **2001**
Keywords: Addition

During their investigations toward a total synthesis of Nodulisporic Acid A, Smith and co-workers (Smith *Org. Lett*. 2001, ASAP) attempted a diastereoselective addition sequence based on the precedent of Koga (Koga, *Tet* 1981, 37, 3951.).



Part A. Provide a mechanism for the transformation of 1 to 2 as reported by Koga (shown below). Be sure your mechanism accounts for the observed stereochemisty.

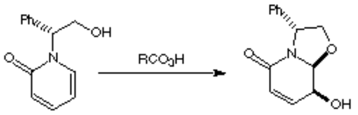
Part B. While attempting to effect an analogous transformation on decalin 3, Smith and co-workers were quite suprised that *cis* diastereomer 4 was obtained. Provide a rationale for the divergent stereochemical outcome.



## Problem 125

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2001**, *3*, 3257-3260
Keywords: Addition

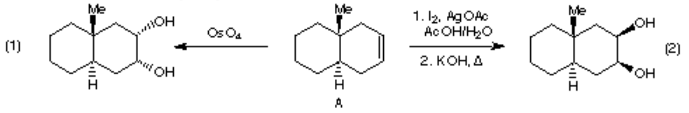
The following reaction was recently reported by Amat and co-workers (*Org. Lett*. 2001, 3, 3257-3260). Provide a mechanism for the this transformation which is consistent with the product stereochemistry. Since stereochemical issues are at stake, carefully rendered 3-D conformational drawings should be incorporated into your answer.



## Problem 127

Contributer: **David A. Evans**
Citation:
Keywords: Addition

If an olefin such as A experiences a facial bias, one may count on steric effects to direct the course of a $OsO_4$ dihydroxylation to the *less hindered olefin diastereoface* (eq 1). Strategically, it is important to be able access the other stereochemical option: dihydroxylation from the *more hindered olefin diastereoface*. This stereochemical option may be implemented through the reaction summarized in equation 2. This reaction has been referred to as the Prevost-Winstein-Woodward dihydroxylation.

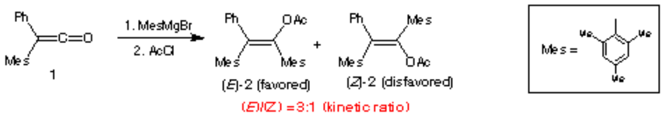


Provide a mechanism for the reaction illustrated in eq 2 in the space below. Since stereochemical issues are at stake, carefully rendered 3-D conformational drawings should be incorporated into your answer.

## Problem 133

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1996**, *118*, 12580
Keywords: Addition

Rappoport has recently reported the transformation illustrated below (*JACS* 1996, *118*, 12580). The kinetic stereochemical outcome of this reaction is superficially unanticipated in that the Grignard reagent adds to ketene 1 from the "more hindered" carbonyl π-face. This value judgement evolves from the assumption that the *mesityl substituent is more sterically demanding than the phenyl substituent*.

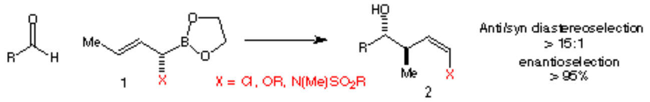


Provide a rationalization for this "contrasteric" ketene addition.

## Problem 134

Contributer: **David A. Evans**
Citation: *Eur, J. Chem.* **2001**, 323
Keywords: Addition

A recent paper by Hoffmann (*Eur. J. Org. Chem.* 2001, 323) highlights important advances made by this laboratory over the years in enantioselective aldehyde allylboration. A typical reaction developed by Hoffmann is illustrated below. In this case the enantiopure allylboronate 1 is transformed into the *anti* adduct 2 with high selectivities. The absolute stereochemical relationships of 1 and 2 are as illustrated.



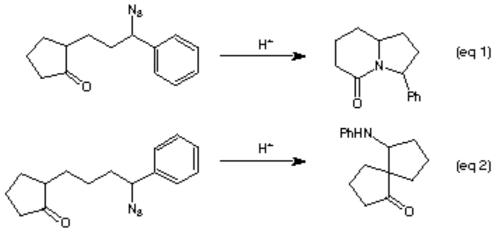
Part A. Draw the obligatory transition state for this transformation below. A carefully rendered three dimensional illustration is requested.

Part B. Identify those hyperconjugative effects, if any, that might be involved in transition state stabilization.

## Problem 141

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2001**, *66*, 886
Keywords: Addition

Aube has recently reported the transformations illustrated below (*J. Org. Chem.* 2001, 66, 886-889). In this study he has documented that the observed product is dependent on the tether length between the azide and carbonyl functional groups.



Part A. Provide a mechanism for the transformation illustrated in Eq 1.

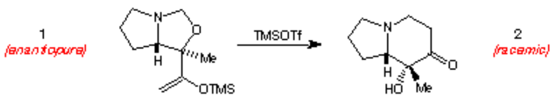
Part B. Provide a mechanism for the transformation illustrated in Eq 2.

Part C. Briefly rationalize the difference in reactivity.

## Problem 142

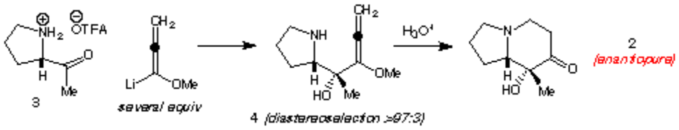
Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1992**, *57*, 1179
Keywords: Addition

During the course of the Overman synthesis of pumilotoxin (*J. Org. Chem.* 1992, *57*, 1179) the indicated transformation was carried out with the expectation that the bicyclic ketone 2 would be enantiopure since the starting amine 1 was enantiomerically pure. Surprisingly, product 2 was obtained as a racemate.



Part A. Provide a mechanism for this transformation that accounts for the illustrated stereochemical outcome.

The revised synthesis of enantiomerically pure 2 is illustrated below (*J. Org. Chem.* 1992, *57*, 1179). Addition of 3 to several equivalents of the illustrated allenyllithium reagent afforded carbonyl adduct 4 as a single diastereomer. This intermediate was then transformed into enantiopure 2 under acidic conditions.



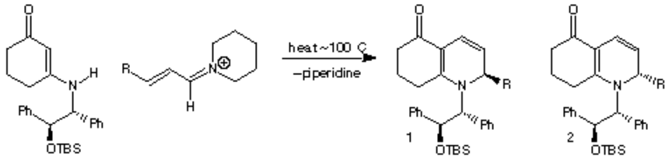
Part B. Provide an explanation for the high level of stereocontrol that is observed in the carbonyl addition step. A three dimensional drawing of the carbonyl addition transition state is requested in conjunction with this answer.

Part C. Provide a mechanism for the transformation of 4 to 2.

## Problem 143

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2000**, *2*, 1161
Keywords: Addition

Hsung and co-workers have recently reported the diastereoselective reaction shown below (*Org. Lett.* 2000, 2, 1161). While there is mechanistic ambiguity associated with this process, the authors have suggested that a pericyclic process is involved in the stereochemistry-determining step, an assumption that is consistent with the sense of asymmetric induction observed in the reaction.



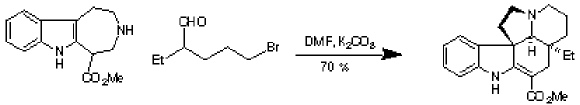
diastereoselection 1 : 2 >10:1

Provide a concise mechanism for this reaction in the space below. Please rationalize the observed sense of asymmetric induction.

## Problem 145

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1978**, *43*, 3705
Keywords: Addition

Martin Kuhne has described a biomimetic approach to the construction of the aspidosperma alkaloid skeleton (*J. Org. Chem.* 1978, *43*, 3705). One of the reactions developed in his laboratory is illustrated below.

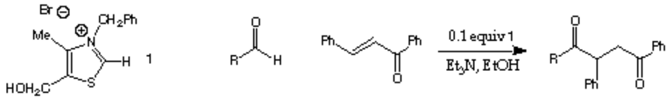


Provide a detailed mechanism for the illustrated transformation.

## Problem 149

Contributer: **David A. Evans**
Citation: *Org. Reactions* **1991**, *40*, 407
Keywords: Addition

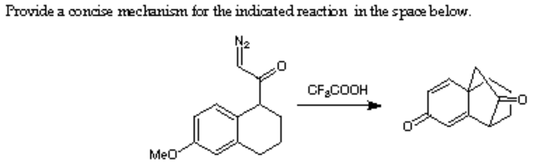
Stetter and coworkers (*Org. Reactions* 1991, *40*, 407) have developed the use of thiazolium salts for the coupling of aldehydes and unsaturated ketones. A typical transformation is illustrated below. The catalyst for this reaction is the thiazolium salt 1.



Provide a concise mechanism for this reaction in the space below.

## Problem 150

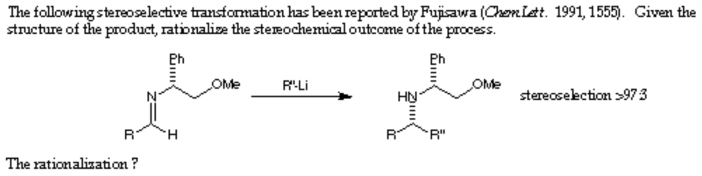
Contributer: **David A. Evans**
Citation:
Keywords: Addition



Provide a concise mechanism for the indicated reaction in the space below.

## Problem 151

Contributer: **David A. Evans**
Citation: *Chem. Lett.* **1991**, 1555
Keywords: Addition

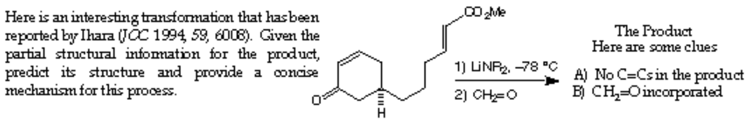


The following stereoselective transformation has been reported by Fujisawa (*Chem Lett.* 1991, 1555). Given the structure of the product, rationalize the stereochemical outcome of the process.

The rationalization ?

## Problem 156

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1994**, *59*, 6008
Keywords: Addition



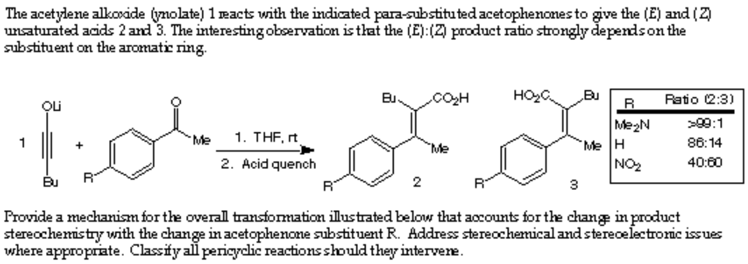
Here is an interesting transformation that has been reported by Ihara (*JOC* 1994, *59*, 6008). Given the partial structural information for the product, predict its structure and provide a concise mechanism for this process.

The Product
Here are some clues

A) No C=Cs in the product
B) CH$_2$=O incorporated

## Problem 160

Contributer: **David A. Evans**
Citation:
Keywords: Addition



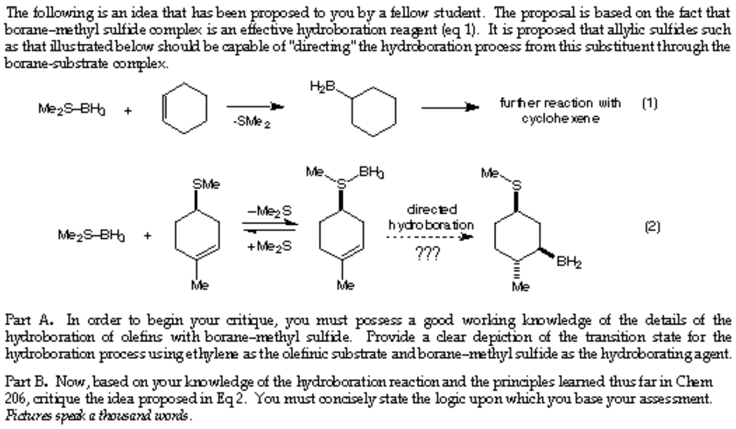
The acetylene alkoxide (ynolate) 1 reacts with the indicated para-substituted acetophenones to give the (*E*) and (*Z*) unsaturated acids 2 and 3. The interesting observation is that the (*E*):(*Z*) product ratio strongly depends on the substituent on the aromatic ring.

| R | Ratio (2:3) |
|---|---|
| Me$_2$N | >99:1 |
| H | 86:14 |
| NO$_2$ | 40:60 |

Provide a mechanism for the overall transformation illustrated below that accounts for the change in product stereochemistry with the change in acetophenone substituent R. Address stereochemical and stereoelectronic issues where appropriate. Classify all pericyclic reactions should they intervene.

## Problem 163

Contributer: **David A. Evans**
Citation:
Keywords: Addition



The following is an idea that has been proposed to you by a fellow student. The proposal is based on the fact that borane–methyl sulfide complex is an effective hydroboration reagent (eq 1). It is proposed that allylic sulfides such as that illustrated below should be capable of "directing" the hydroboration process from this substituent through the borane-substrate complex.

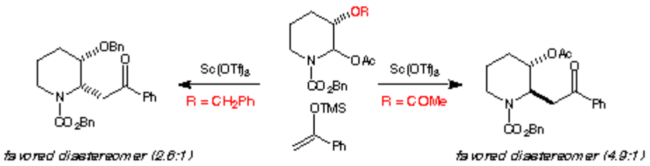
Part A. In order to begin your critique, you must possess a good working knowledge of the details of the hydroboration of olefins with borane–methyl sulfide. Provide a clear depiction of the transition state for the hydroboration process using ethylene as the olefinic substrate and borane–methyl sulfide as the hydroborating agent.

Part B. Now, based on your knowledge of the hydroboration reaction and the principles learned thus far in Chem 206, critique the idea proposed in Eq 2. You must concisely state the logic upon which you base your assessment. *Pictures speak a thousand words.*

## Problem 165

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2001**, *66*, 809-823
Keywords: Addition

Kobayashi has recently reported the illustrated diastereoselective addition reactions (*J. Org. Chem.* 2001, 66, 809-823). This study reports that reaction diastereoselection may be controlled by the nature of the oxygen substituent at the 3-position of the piperidine ring.

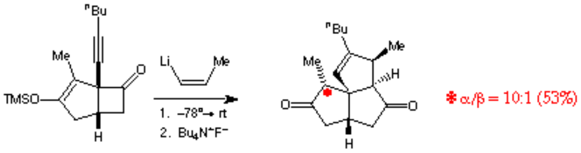


Provide an explanation for these observations in the space below.

## Problem 170

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2000**, *65*, 8564
Keywords: Addition

Moore has recently reported the illustrated reaction cascade which rapidly leads to the assemblage of the illustrated tricyclic diketone (*J. Org. Chem.* 2000, 65, 8564).

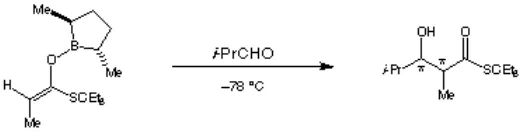


Provide a concise mechanism for the illustrated reaction sequence in the space below.

## Problem 173

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1986**, 8297
Keywords: Addition

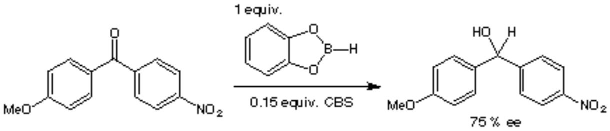
Provide a clear depiction of the transition state which predicts the product stereochemistry at the starred (*) carbon atoms (Masamune, *JACS*, **1986**, 8279).



## Problem 174

Contributer: **David A. Evans**
Citation: *Angew. Chem.* **1998**, 1987
Keywords: Addition

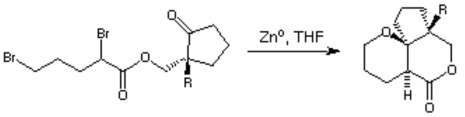
Corey's CBS catalyst for ketone reduction often delivers high yields of enantioenriched secondary alcohols (*ACIE*, 1998, 1987). Provide a clear clear illustration of the transition state which predicts the absolute stereochemistry of the product obtained in the illustrated reaction. Include an explanation of why the reduction of this practically symmetric ketone is selective.



## Problem 179

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1989**, 1530
Keywords: Addition

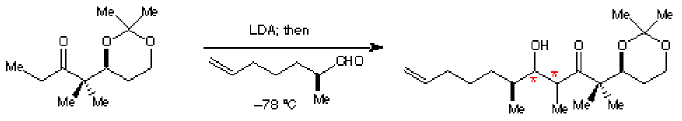
Provide a mechanism that accounts for observed stereochemistry of the illustrated transformation (Heathcock, *JACS*, 1989, 1530).



## Problem 180

Contributer: **David A. Evans**
Citation: *Angew. Chem.* **1997**, *36*, 523
Keywords: Addition

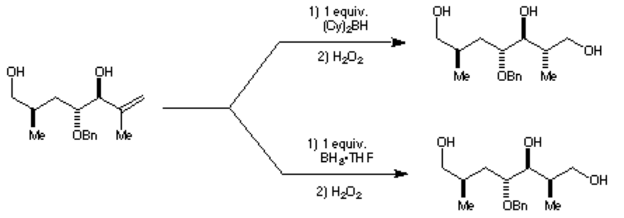
Provide a mechanism which clearly predicts the product stereochemistry at the starred (*) carbon atoms (Schinzer, *ACIEE*, 1997, 36, 523). Provide a clear depiction of the transition state to support your answer.



## Problem 182

Contributer: **David A. Evans**
Citation:
Keywords: Addition

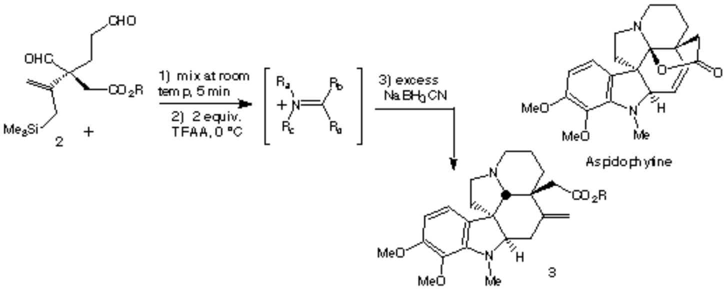
Provide clear three-dimensional depictions of the transition states for the following hydroborations. Specifically point out each factor responsible for the observed turnover in selecivity (Tatsuda, *TL*, 1991, 6015).



## Problem 185

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1999**, *121*, 6771
Keywords: Addition

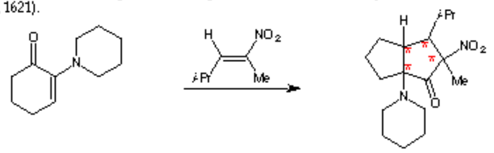
During Corey's recent synthesis of Aspidophytine (*JACS* 1999, *121*, 6771), the pivotal intermediate 3 was assembled by the union of 1 and 2 under the specified conditions. Provide a mechanism for this single-pot transformation.



## Problem 188

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1983**, 1621
Keywords: Addition

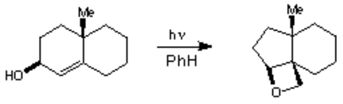
Provide a mechanism for the following reaction that predicts the stereochemistry at the starred (*) carbon atoms (Valentin, *TL*, 1983, 1621).



## Problem 190

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1971**, 214
Keywords: Addition

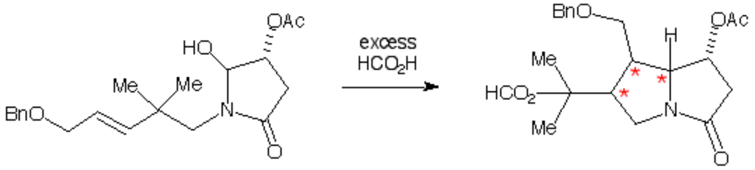
Provide a mechanism for the following transformation that explains the observed stereochemistry (Marshall, *JOC*, 1971, 214).



## Problem 193

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1985**, 235
Keywords: Addition

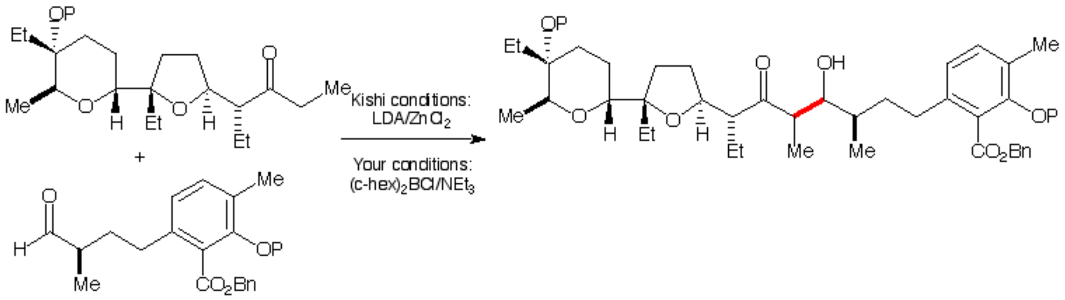
Provide a mechanism for the indicated transformation that predicts the observed stereochemistry at the three starred (*) carbon atoms (*JOC*, **1985**, 235).



## Problem 194

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1978**, 2933
Keywords: Addition

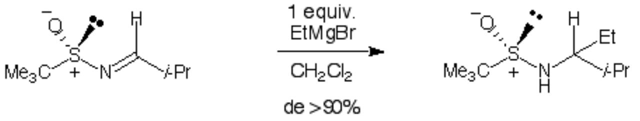
In the Kishi Lasalocid A synthesis, the illustrated aldol fragment coupling proceeded with only moderate stereoselectivity (*JACS*, **1978**, 2933). If you were planning this fragment coupling today, you would probably choose (c-hex)$_2$BCl / NEt$_3$ which would cleanly provide the (E) boron enolate (Brown *JACS* **1989**, *111*, 3441). What product stereochemistry would you expect from your reaction? Include a transition state drawing to support your answer. Point out the specific factors responsible for your predicted selectivity. Is your reaction a fully matched or partially matched aldol reaction?



## Problem 196

Contributer: **David A. Evans**
Citation: *Tetrahedron* **1999**, 8883
Keywords: Addition

**Part A.** Provide a mechanism for the following reaction (*Tetrahedron*, **1999**, 8883). Include a clear transition state representation that predicts the major product diastereomer.

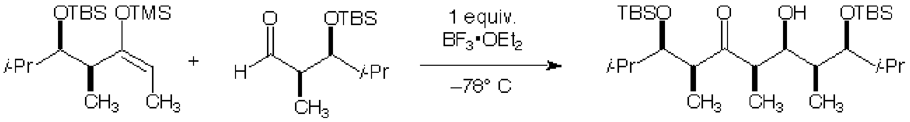


**Part B.** When the reaction is performed in diethyl ether or THF, the diastereoselectivity is significantly lowered. Propose an explanantion for this observation.

## Problem 197

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1995**, 9598
Keywords: Addition

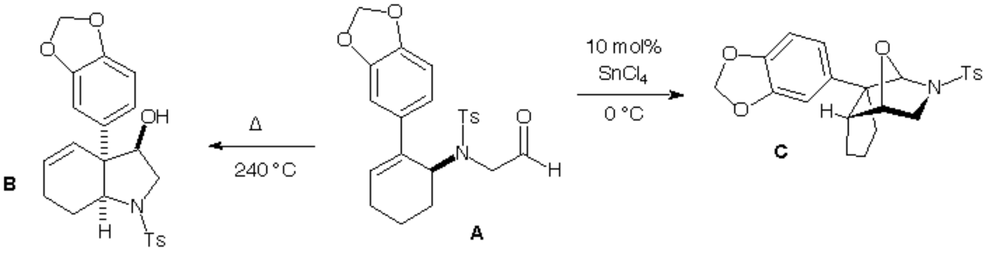
Provide a mechanism for the following monodentate Lewis acid promoted aldol reaction. Include a transition state representation, indicating the specific factors that are responsible for the observed selectivity (*JACS*, **1995**, 9598).



## Problem 203

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1998**
Keywords: Addition

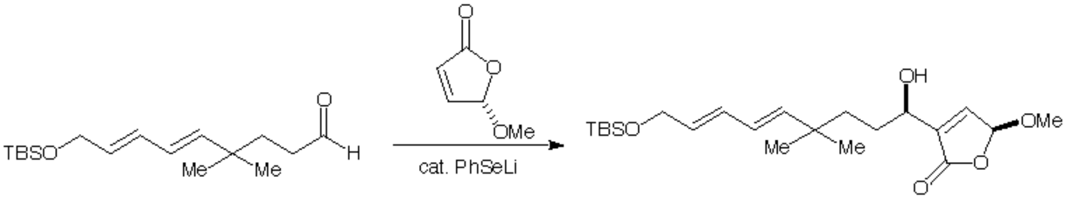
Provide mechanisms that account for the stereoselective formation of the products obtained by treatment of aldehyde **A** to the conditions shown below. Briefly comment on the difference in reactivity under the two sets of conditions (*JOC*, **1998**, 7586).



## Problem 204

Contributer: **David A. Evans**
Citation: *SynLett* **1999**, 1325
Keywords: Addition

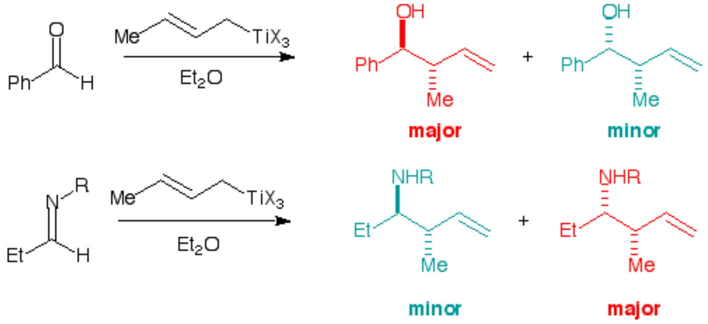
Provide a mechanism for the following reaction that explains the observed reaction diastereoselectivity (*Synlett*, **1999**, 1325). Be sure your mechanism accounts for the catalytic nature of PhSeLi.



## Problem 205

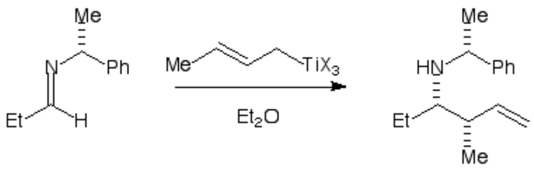
Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1995**, 3881
Keywords: Addition

Crotyl titanium reagents have been developed for addition to C=O and C=N bonds (*J. Am. Chem. Soc.* **1995**, 3881 and *J. Org. Chem.* **1995**, 8136).



**Part A.** Provide an explanation, including clear 3D drawings of the transition states, which account for the divergent stereoselectivity observed in the addition reactions illustrated above.

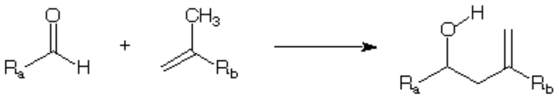
**Part B.** The use of a chiral imine induces useful levels of asymmetric induction in this reaction. Provide an explanation, including a clear 3D drawing of the transition state, which accounts for the preferred production of the indicated diastereomer.



## Problem 210

Contributer: **David A. Evans**
Citation:
Keywords: Addition

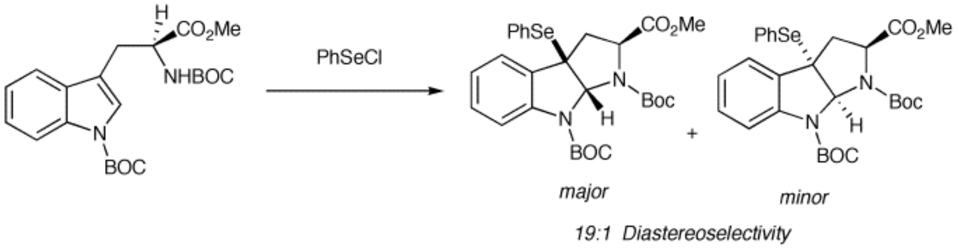
The carbonyl ene reaction is illustrated below. Using FMO analysis, evaluate the transition state of this reaction. Your answer should include: a transition state drawing; clear orbital depictions and HOMO-LUMO assignments; an indication of the number of electrons from each segment; and indication of whether the reaction is thermally allowed.



## Problem 222

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1999**, *121*, 11953
Keywords: Addition

Provide a mechanism for the following reaction and explain the stereoselectivity. (Danishefsky, *JACS* **1999** 121, 11953)

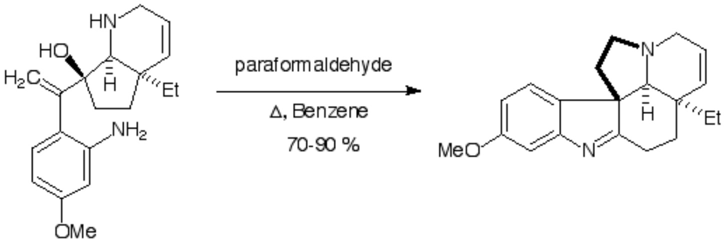


**Answer:**

## Problem 225

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1983**, *48*, 2685
Keywords: Addition

One of the most innovative reactions which results in the construction of the aspidosperma alkaloid skeleton has recently been reported by Professor L. Overman (*JOC* **1983**, *48*, 2685). Provide a concise mechanism for this reaction.

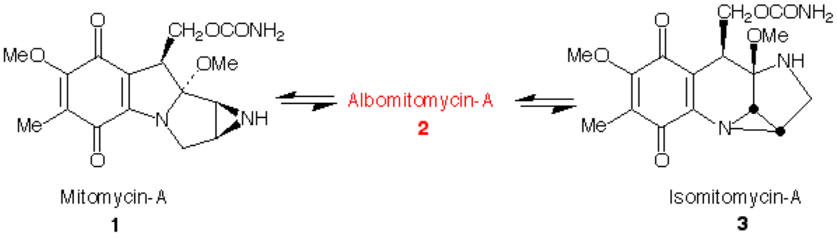


## Problem 226

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1987**, *109*, 7881
Keywords: Addition

The Fukuyama synthesis of the mitomycins (*JACS* **1987**, *109*, 7881) proceeds through the intriguing rearrangement shown below. This transformation, which was first documented by Kono and co-workers (*JACS* **1987**, *109*, 7224) occurs upon dissolving either **1**, **2**, or **3** in methanol over a two-day period. The equilibrium mixture, which may be approached from any one of the three constituents, favors the mitomycin skeleton (Ca 90%).

Draw a detailed mechanism for the conversion of **3** ⇒ **2** ⇒ **1** and clearly identify the structure of albomitomycin-A.

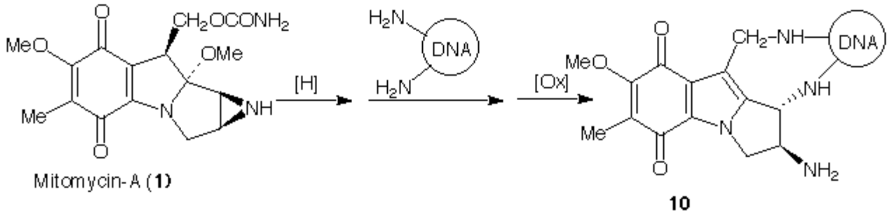


Please not that problems 226-229 are all coupled they may be retrieved by using the "**Synthesis**" plus "**Natural Product**" descriptors

## Problem 229

Contributer: **David A. Evans**
Citation: *Science* **1987**, *235*, 1204
Keywords: Addition

Nakanishi, Verdine and co-workers have shown that Mitomycin-C (**1**) is a bio-alkylating agent which is known to selectively crosslink DNA, *Science* **235**, 1204 (1987). The probable mechanism by which this compound functions in this capacity has been also examined by Danishefsky, *J. Am. Chem. Soc.* **108**, 4648 (1986). He has shown that Mitomycin-C must be "primed" by reduction before it can function as an effective alkylating agent. Overall, some of the events associated with DNA crosslinking are outlined below.
Provide a detailed mechanism for the overall transformation of **1** ⇒ **10** . There is more than one sequence of events that is possible; however, you only need to show one to receive full credit.

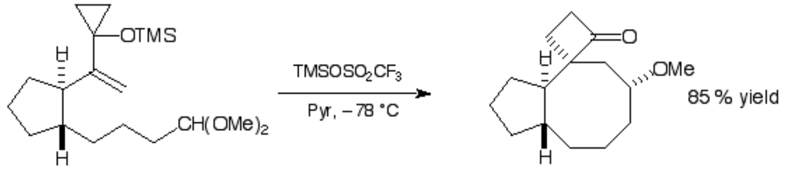


Please not that problems 226-229 are all coupled they may be retrieved by using the "**Synthesis**" plus "**Natural Product**" descriptors

## Problem 230

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1986**, *110*, 6556
Keywords: Addition

Write a plausible mechanism for the reaction illustrated below. Where stereochemistry is an issue, draw the conformation of the reacting entity which illustrates the relationship between chiral and prochiral centers.

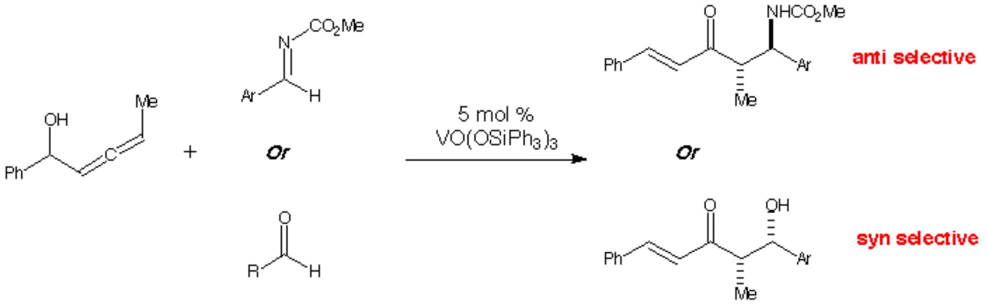


Trost & Co-workers, *JACS*, **110**, 6556 (1988).

## Problem 232

Contributer: **David A. Evans**
Citation: *Angew. Chem.* **2003**, *42*, 2063
Keywords: Addition

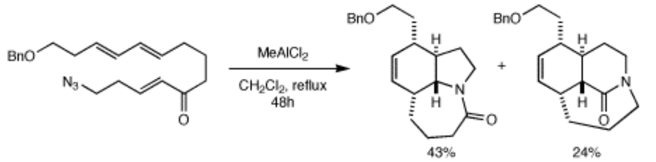
Trost *et. al.* have reported an interesting vandium catalyzed diastereoselective addition of allenols to imines and aldehydes (*Angew. Chem. Int. Ed.* **2003**, *42*, 2063). Propose a reasonable mechanism and a model accounting for the observed stereoselection. **Also see Problem 111. It is related.**



## Problem 240

Contributer: **Carl A. Morales**
Citation: *Angew. Chem.* **2002**, *41*, 4492
Keywords: Addition

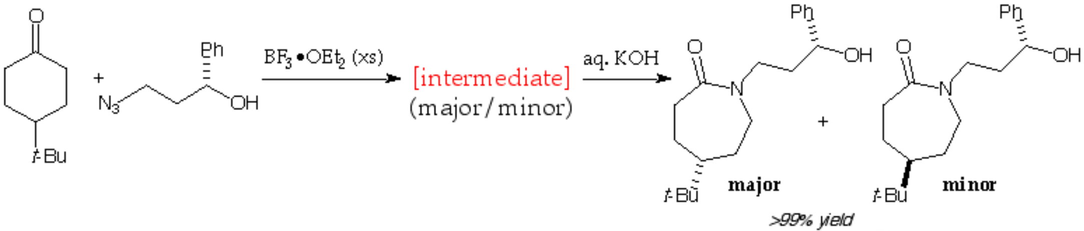
In a recent report of a formal synthesis of stenine, researchers reported a tandem polycyclization which afforded the following major and minor products. Please propose a mechanism for this transformation which accounts for both products, their relative stereochemistry, and their relative distribution.



## Problem 250

Contributer: **Jake Janey**
Citation: *J. Am. Chem. Soc.* **2003**, *125*, ASAP
Keywords: Addition

Aubé recently reported an asymmetric ring expansion of achiral cyclohexanones with enantiopure hydroxyalkyl azides to give enantioenriched caprolactams (*Org. Lett* **1999**, *1*, 495 and *J. Am. Chem. Soc.* **2003** ASAP). One of his reported transformations is illustrated below. The paper includes related examples with other 1,3- and 1,2-hydroxyalkyl azides and various cyclohexanones.

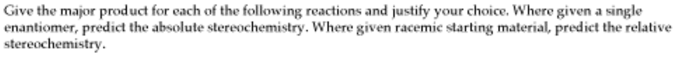


*>99% yield*
*diastereoselection 95:5*

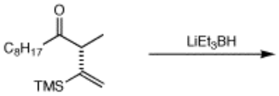
Provide a plausible mechanism for this reaction. Your answer should include three-dimensional structures that rationalize the observed stereoselection.

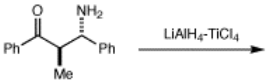
## Problem 252

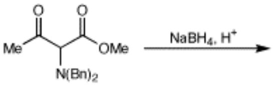
Contributer: **Carl A. Morales**
Citation:
Keywords: Addition

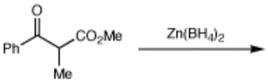


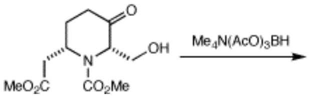
Give the major product for each of the following reactions and justify your choice. Where given a single enantiomer, predict the absolute stereochemistry. Where given racemic starting material, predict the relative stereochemistry.





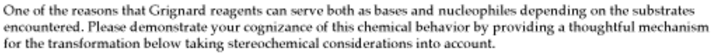




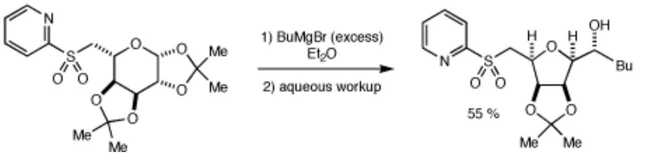


## Problem 273

Contributer: **Carl A. Morales**
Citation: *Tetrahedron Lett.* **1994**, *35*, 8377
Keywords: Addition

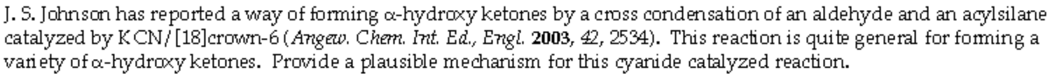


One of the reasons that Grignard reagents can serve both as bases and nucleophiles depending on the substrates encountered. Please demonstrate your cognizance of this chemical behavior by providing a thoughtful mechanism for the transformation below taking stereochemical considerations into account.

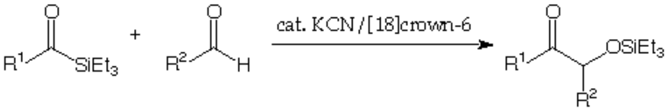


## Problem 280

Contributer: **Jake Janey**
Citation: *Angew. Chem.* **2003**, *42*, 2534-2536
Keywords: Addition



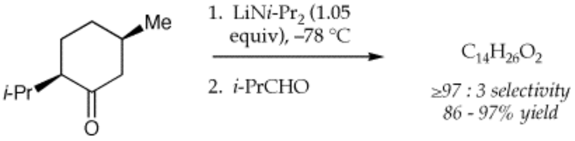
J. S. Johnson has reported a way of forming α-hydroxy ketones by a cross condensation of an aldehyde and an acylsilane catalyzed by KCN/[18]crown-6 (*Angew. Chem. Int. Ed., Engl.* **2003**, *42*, 2534). This reaction is quite general for forming a variety of α-hydroxy ketones. Provide a plausible mechanism for this cyanide catalyzed reaction.



## Problem 300

Contributer: **Keith Woerpel**
Citation: *Tetrahedron Lett.* **1997**, *38*, 9043
Keywords: Addition

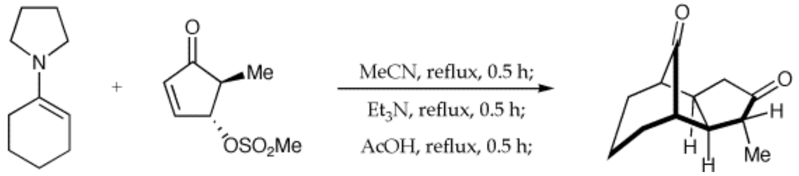
Isomenthone (7) has been subjected to the following reaction (J. M. Gardiner, *Tetrahedron Lett.* **1997**, *38*, 9043). Provide the product of this reaction, including the stereochemistry at all relevant stereogenic centers. Draw a transition structure that clearly indicates how this stereoisomer is formed.



## Problem 302

Contributer: **Keith Woerpel**
Citation: *J. Am. Chem. Soc.* **1997**, *119*, 2066
Keywords: Addition

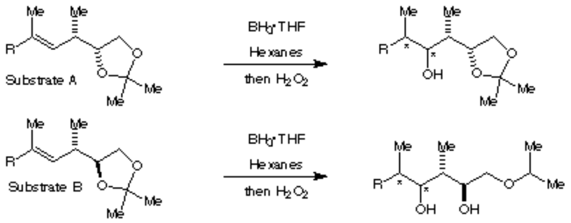
West provided several examples of an one-flask annulation reaction that provides bridged bicyclic products with high diastereoselectivity and yield (F. G. West *J. Am. Chem. Soc.* **1997**, *119*, 2066). Provide a mechanism for the following example.



## Problem 309

Contributer: **David A. Evans**
Citation: *SynLett* **1993**, 696
Keywords: Addition

The indicated olefins were subjected to hydroboration /oxidation as shown (*Synlett*, 1993, 696).

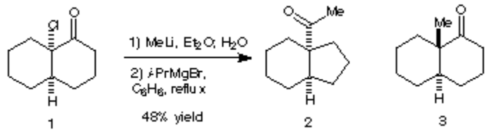


Part A. Please predict the major stereoisomer obtained from these reactions and illustrate your predictions with clear 3D drawings.
Part B. Please also explain the fact that B suffers reductive ring opening while A does not..

## Problem 310

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1972**, *37*, 4090
Keywords: Addition

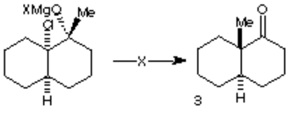
Sisti and Citale (*J. Org. Chem.* 1972, *37*, 4090) have reported that cis chlorodecalone (1) was treated with methyllithium and a mixture of stereoisomeric alcohols was isolated. When this mixture of alcohols was converted to the derived magnesium alkoxides and heated in benzene, the ring contracted product (2) was isolated in 48% overall yield. It is interesting that none of the trans methyldecalone (3) was observed.



Not isolated

Part A. Rationalize the formation of 2 from both diastereomeric alcohols derived from 1. Please use carefully rendered three dimensional drawings to illustrate your answer.

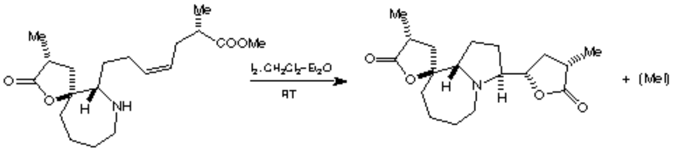
Part B. Explain why the indicated alkoxide does not lead to the formation of 3.



## Problem 311

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1986**, *111*, 1923
Keywords: Addition

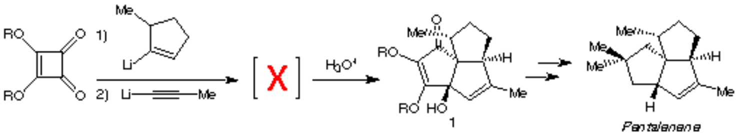
The iodine-induced transformation shown below is a key step in the Williams synthesis of croomine (*JACS* 1989, *111*, 1923). Given the stereochemical outcome of the illustrated transformation, propose a detailed mechanism for this reaction sequence. Williams has recently provided another closely reaction of the same design (*Org. Lett* 2003, *5*, 3361).



## Problem 328

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2002**, *4*, 4547-4549
Keywords: Addition

A synthesis of the hydrocarbon pentalenene was recently disclosed by Paquette and co-workers (*Org. Lett.* 2002, *4*, 4547-4549). The pivotal reaction cascade that affords the pentalenene core 1 is illustrated below.

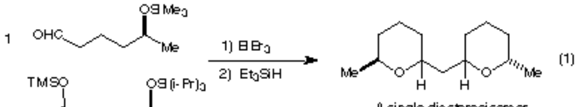


Please provide a mechanism for the reaction cascade that results in the production of the tricyclic core 1. Your answer should include clear 3-D drawings where relevant and should clearly identify intermediate X.

## Problem 329

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2003**, *125*, 11456-11457
Keywords: Addition

P. A. Evans and co-workers have recently reported a highly diastereoselective approach to the construction of linked tetrahydropyrans (*JACS* 2003, *125*, 11456-11457). One of their cases is illustrated in Eq 1. In this transformation $BiBr_3$ is employed as a mild Lewis acid.



(1)

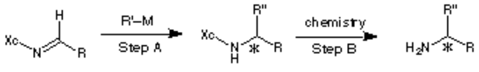
A single diastereoisomer
diastereoselection ≥95:5 (73% yield)

Please provide a mechanism for the reaction cascade that results in the production of the illustrated product. Your answer should include clear 3-D drawings where relevant and should provide the stereochemistry of the major product diastereoisomer.

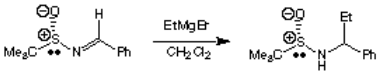
## Problem 330

Contributer: **David A. Evans**
Citation: *Tetrahedron* **1999**, *55*, 8883
Keywords: Addition

Chiral auxiliaries (Xc) are routinely employed to control the absolute stereochemistry of the addition or organometallic reagents to imines (Step A). A design requirement of these controllers is that they may be readily cleaved after the addition step (Step B). In the two parts of this question posed below are presented two well-established chiral controllers that employ chelate organization as an integral part of lthe chirality transfer process.

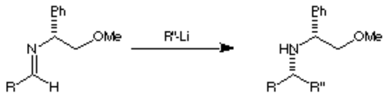


Part A. Provide a mechanism for the following transformation reported by Ellman and co-workers. (*Tet*, 1999, 8883). Include a clear transition state representation that predicts the major product diastereomer. Clearly illustrate the the absolute stereochemistry of the product.



diastereomer ratio 92:8

Part B. The following stereoselective transformation has been reported by Fujisawa (*Chem. Lett.* 1991, 1555). Given the stereostructure of the product, rationalize the stereochemical outcome.

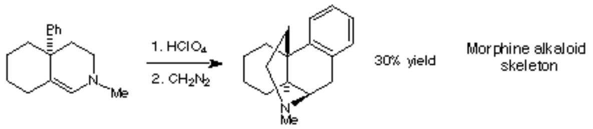


diastereomer ratio >97:3

## Problem 333

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1980**, *102*, 5955-5956
Keywords: Addition

Evans and Mitch have reported reported the short approach to the synthesis of the morphine skeleton (*JACS* 1980, *102*, 5956).

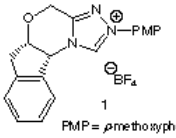


Provide a mechanism for this interesting transformation.

## Problem 334

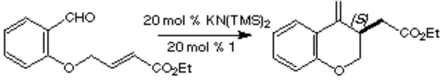
Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2002**, *124*, 10298
Keywords: Addition

The development of chiral variants of the Stetter reaction is a current objective in the chemical literature. Such a study has been recently reported by Rovis and Co-workers (*JACS* 2002, *124*, 10298). In the presence of 20 mol percent of triazolium salt 1, and an equal amount of $KN(TMS)_2$, 2 is transformed into 3 in 94% yield and 95% ee.



1

PMP = *p*-methoxyphenyl



2

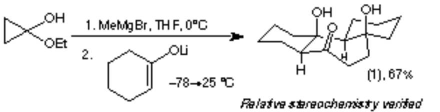
3, 94% yield; 95% ee

Provide a mechanism for this rearrangement in the space below. You do not need to account for the absolute stereochemical outcome of this reaction in your answer.

## Problem 337

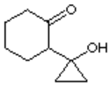
Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1986**, *108*, 8313
Keywords: Addition

Helquist has reported the interesting enolate-based ring-forming process illustrated below (*JACS* 1986, *108*, 8313). In this experiment, the MeMgBr was added to the cyclopropanone hemiketal. The cyclohexanone enolate (2 equiv) was then cannulated into the reaction vessel. In addition to the indicated product 1, ~14% of the cyclopropanone aldol adduct 2 was obtained. If 2 is treated under the stated reaction conditions, an 80% of 1 is obtained. The selection of Mg(II) to mediate the stereochemical outcome of this reaction is important.



(1), 67%

*Relative stereochemistry verified by x-ray crystallography*



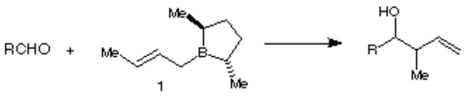
(2), 14%

Please provide a plausible mechanism for this transformation. Use 3-dimensional representations where appropriate to illustrate your answer.

## Problem 339

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1987**, *52*, 4831
Keywords: Addition

The $C_2$-symmetric allyl borane 1 introduced by Masamune (*J. Org. Chem.* 1987, *52*, 4831) has had an important impact on the design of chiral aldol and allylation catalysts.



Box-1

Provide the absolute stereochemistry of the product of this reaction in Box-1.
Provide a 3-dimensional drawing of the transition state for this reaction in Box-2.

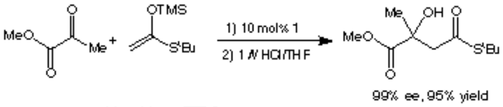
‡

Box-2

## Problem 340

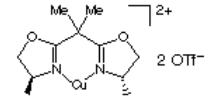
Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1999**, *121*, 686
Keywords: Addition

The $C_2$-symmetric cationic Cu(II) complex 1 is a chiral Lewis acid catalyst that exhibits good chelating potential. The utilization of 1 in the catalyzed Mukaiyama aldol addition is illustrated below (*JACS* 1999, *121*, 686).



99% ee, 95% yield

Box-1



1

‡

Provide the absolute stereochemistry of the product of this reaction in Box-1.
Provide a 3-dimensional drawing of the transition state for this reaction in Box-2.

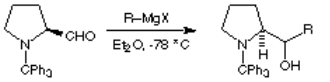
*Hint: Cu(II) complexes strongly prefer square-planar geometries*

Box-2

## Problem 341

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2003**, *68*, 9747
Keywords: Addition

The illustrated stereoselective Grignard additions to trityl-protected prolinal have recently been reported (*JOC*, 2003, *68*, 9747). These additions proceed with exceptional stereochemical control. A clue as to the operational mechanism for stereocontrol follows from the observation that the allylation product produced by Grignard addition has the same stereochemistry as the allylation product produced by the addition of allylsilane/$BF_3 \cdot OEt_2$.



*diastereoselection ≥98:2*

Box-1

Please draw the absolute stereochemistry of the product in Box-1. In Box-2 provide a three-dimenional representation of the transition state for this reaction that rationalizes the diastereoselection for this process. Briefly identify the transition state stereochemical control element(s) below.

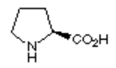
‡

Box-2

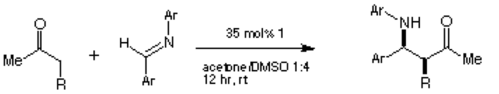
## Problem 342

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2002**, *124*, 827
Keywords: Addition

The illustrated proline-catalyzed Mannich reaction was recently reported by B. List (*JACS* 2002, *124*, 827). This reaction proceeds with exceptional stereochemical control.



L-proline (1)



92 yield, dr >20:1, ee >99%

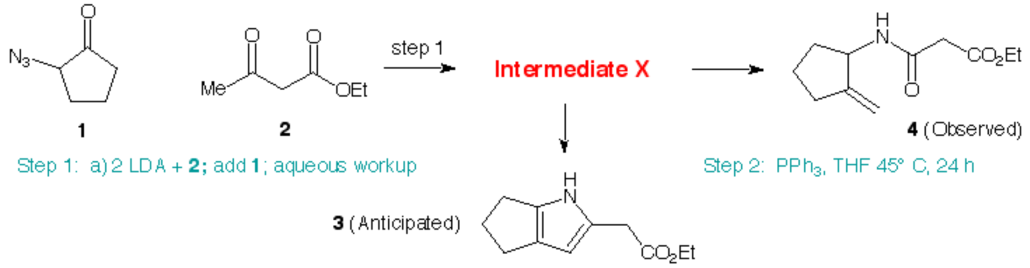
Provide a three-dimenional representation of the transition state for this reaction that rationalizes the diastereo and enantioselection for this process. Briefly identify the transition state stereochemical control elements.

‡

## Problem 343

Contributer: **David A. Evans**
Citation: *Chem. Commun.* **2003**, 3044
Keywords: Addition

Langer and co-workers recently reported the interesting *errant* Staudinger reaction illustrated below ( *Chem Comm.* **2003**, 3044). The anticipated reaction product was pyrrole **3** while the observed product was **4**.



Step 1: a) 2 LDA + **2; add 1**; aqueous workup

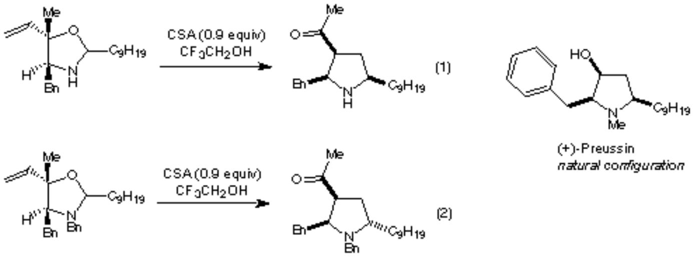
Step 2: $PPh_3$, THF 45° C, 24 h

Provide a detailed mechanism for this transformation.

## Problem 359

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.*
Keywords: Addition

An elegant enantiodivergent synthesis of the potent anti-fungal reagent Preussin was reported by Overman (*JACS* 1994, 11241.).



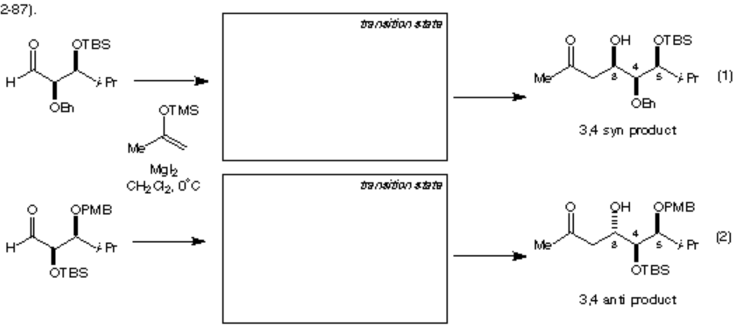
Part A. Provide a mechanism for the transformation illustrated in Eq 1. Where stereochemicasl issues are involved, 3-dimensional drawings should be employed.

Part B. Provide a mechanism for the transformation illustrated in Eq 2. Where stereochemicasl issues are involved, 3-dimensional drawings should be employed.

## Problem 362

Contributer: **David A. Evans**
Citation: **2003**
Keywords: Addition

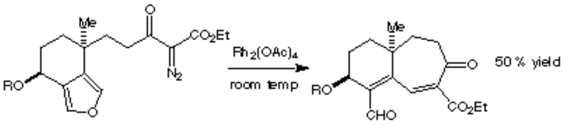
The two illustrated $MgI_2$–promoted Mukaiyama aldol reactions occur with high diastereoselectivity (Eq 1, 2). In contrast, only poor selectivity is observed in both reactions when $MgI_2$ is replaced with $BF_3 \cdot OEt_2$. Provide a transition state model that explains the formation of the 3,4 syn product in (Eq 1) and the 3,4 anti product in (Eq 2). Assume that the Bn and PMB protecting groups are chemically equivalent. (Victor Cee, Ph.D. Thesis, Harvard Unifversity, 2003, pgs. 82-87).



## Problem 368

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2003**, *5*, 4113
Keywords: Addition

The following transformation was recently reported by Trauner and co-workers (*Organic Lett.* 2003, *5*, 4113) as a pivotal reaction in the synthesis of specific members of the guanacastepene diterpenes. These natural products have attracted interest as potent antibiotics against *Staphylococcus aureus*.

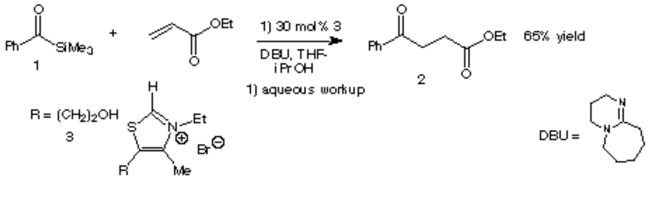


Provide a mechanism for the transformation illustrated above.

## Problem 369

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2004**, *ASAP*,
Keywords: Addition

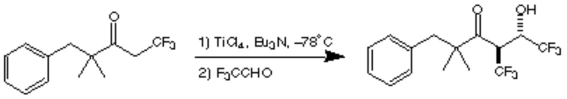
The first example of a "Silyl-Stetter reaction" will appear in the literature shortly (Scheidt, *JACS* 2004, 125, in press). Provide a mechanism for this transformation.



## Problem 379

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2003**, *5*, 4807
Keywords: Addition

Mikami and co-workers have recently reported the illustrated aldol reaction (*Organic Lett.* 2003, *5*, 4807). This result was unexpected in light of the fact that the intervening (Z) enolate geometry was unequivocally established. The authors conclude that "dipole effects" are responsible for the observed stereochemical outcome. Please reproduce the authors' rationale for the observed reaction diastereoselection.

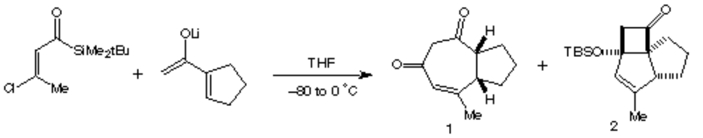


83% yield, 81% de

## Problem 380

Contributer: **David A. Evans**
Citation: *Organic Lett.* **1999**, 677
Keywords: Addition

Takeda and co-workers have developed an efficient strategy for the synthesis of fused 5,7 ring systems by reacting acylsilanes with lithium enolates (*Org. Lett.*,1999, 677). Although the 5,7 bicyclic product 1 is often observed, the nature of the enolate nucleophile can affect the course of the reaction.



1 35%

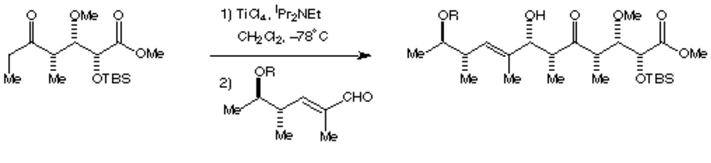
2 25%

Provide a mechanism for the formation of both the anticipated 5,7 bicycle 1 and the tricyclic ketone 2.

## Problem 381

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2002**, *4*, 4739
Keywords: Addition

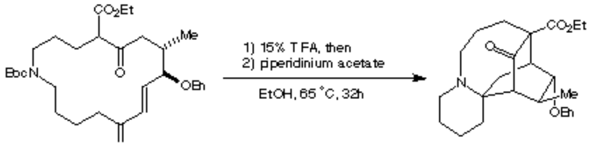
In 2002 Roush reported the stereoselective synthesis of the C1–C12 fragment of Tedanolide (*Organic Lett.* 2002, *4*, 4739). The illustrated aldol reaction was employed. Provide a clear 3-D transition state which rationalizes the stereoselectivity of this reaction.



## Problem 382

Contributer: **Jonathan Scheerer**
Citation: *Angew. Chem.* **2005**, *44*, 6038-6042
Keywords: Addition

Provide a clear mechanism for the illustrated reation.

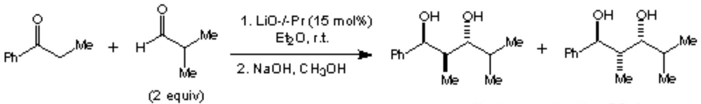


*Evans et al. unpublished results, 2003.*

## Problem 385

Contributer: **David A. Evans**
Citation: *Organic Lett.* **1999**, *1*, 1427
Keywords: Addition

The following one-pot Aldol-Tishchenko reaction reported by Morken (*Org. Lett.*, 1999, 1427) for the production of propionate substrates occurs with high diastereoselectivity. Provide a stereochemical model to explain the observed syn-anti product.

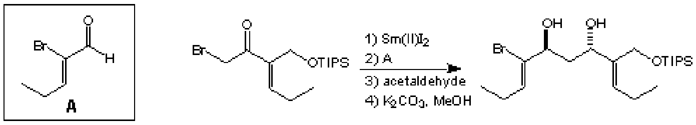


diastereoselection 96:4

## Problem 386

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2002**, *4*, 3087
Keywords: Addition

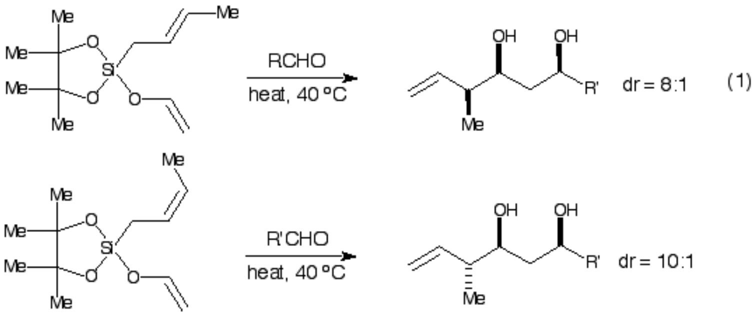
A recent paper by Wood and co-workers presented the one-pot transformation shown below (*Org. Lett.* 2002, *4*, 3087). In the space provided, please propose a mechanism that explains the relative stereochemistry of the product diol.



## Problem 392

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2002**, *124*, 10672
Keywords: Addition

The following transformation was recently reported by Leighton (*J. Am. Chem. Soc* **2002**, *124*, 10672).

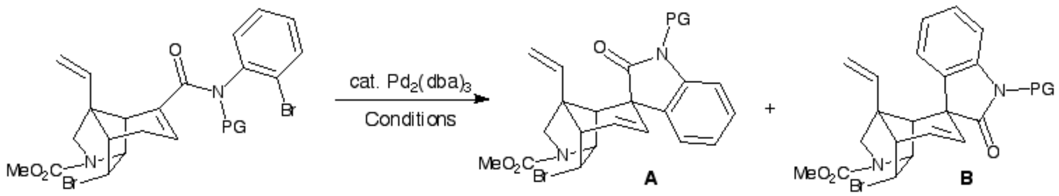


Provide a plausible mechanism for this transformation in the space below:

## Problem 395

Contributer: **Andre Beauchemin**
Citation: *Tetrahedron Lett.* **1992**, *33*, 4859
Keywords: Addition

The Heck reaction is a powerful method to form C-C bonds and an efficient approach to the formation of quaternary carbon centers . A specific example is shown below (Madin and Overman, *TL* **1992**, *33*, 4859).



| Conditions | **A : B** |
|---|---|
| $Et_3N$ (10 equiv), toluene, 110 °C | 89:11 |
| $Ag_3PO_4$ (2 equiv), THF, 66 °C | 3:97 |

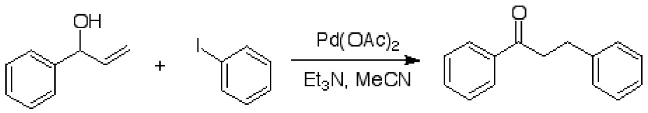
**1. Postulate a catalytic cycle for this reaction.**

**2. Provide a rationale for the divergent stereochemical outcome.**

## Problem 398

Contributer: **Andre Beauchemin**
Citation: *Tetrahedron* **2001**, *57*, 7449
Keywords: Addition

The Heck reaction is one of the most powerful transition metal C–C bond forming reactions (Whitcombe, et al, *Tetrahedron* **2001**, *57*, 7449). A typical example of this transformation is shown below.

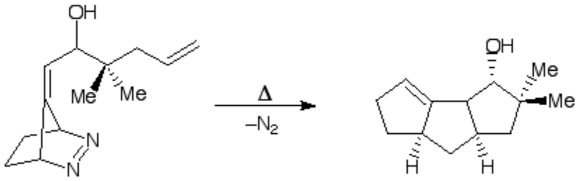


Provide a plausible mechanism for this transformation and illustrate the individual steps in the catalytic cycle with a series of balanced equations. *Note: Pd(OAc)$_2$ is reduced to form Pd(0) under the reaction conditions. Do not concern yourself with this reduction step.*

## Problem 402

Contributer: **Phillip S. Baran**
Citation: *Chem. Rev.* **1986**, *86*, 875
Keywords: Addition

Little and co-workers employed this stunning transformation in a series of studies directed toward the synthesis of diketocoriolin B. (For a relevant review see *Chem. Rev.* **1986**, *86*, 875).

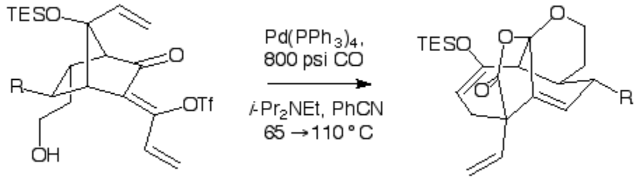


Please provide a mechanism for this transformation, accounting for stereochemistry when necessary.

## Problem 404

Contributer: **Phillip S. Baran**
Citation: *Organic Lett.* **2000**, *2*, 2905
Keywords: Addition

Leighton and Bio have recently disclosed the following approach to the core of CP-263,114 ( *Org. Lett* **2000**, 2905).

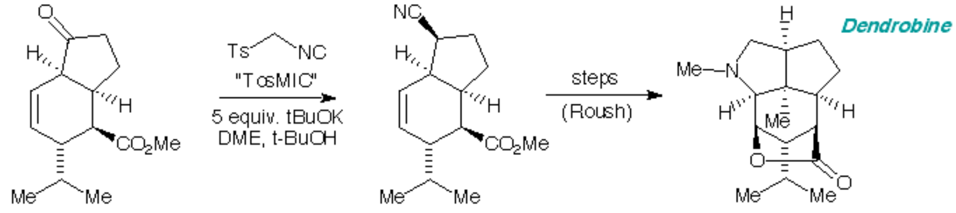


Please provide a mechanism for this transformation.

## Problem 409

Contributer: **Dan O,Malley**
Citation: *J. Org. Chem.* **1977**, *42*, 3114
Keywords: Addition

Tosylmethyl isocyanate (TosMIC) is a remarkable reagent developed by van Leusen and co-lworkers at the University of Groningen. One use of this reagent is for the one-carbon homologation of ketones to nitriles as illustrated below (*J. Org. Chem.* **1977**, *19*, 3114). In the illustrated application, Roush has applied this methodolgy to his synthesis of dendrobine (*J. Am. Chem. Soc.* **1980**, *4*, 1390).

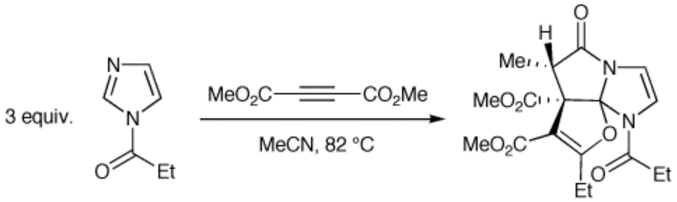


Provide one or more plausible mechanisms for this transformation.

## Problem 413

Contributer: **Narendra Ambhaikar**
Citation: *SynLett* **1991**, 241
Keywords: Addition

Knölker and co-workers *Syn Lett.* **1991**, *4*, 241) have reported the diastereoselective annulation of 2-propanoylimidazole with dimethylacetylenedicarboxylate (DMAD) to yield the complex heterocycle shown below.

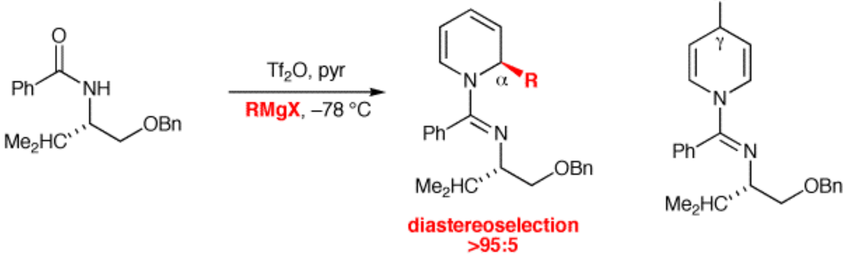


Provide a detailed mechanism for this reaction.

## Problem 434

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2001**, *123*, 11829
Keywords: Addition

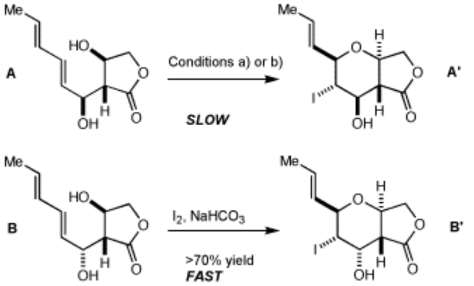
Charette and co-workers recently reported a creative approach to the enantioselective synthesis α-substituted piperidine derivatives illustrated below *(JACS* **2001,** *123,* 11830). The alpha regioselectivities are generally >10:1 while the alpha diastereoselections are reported to be >95:5. Provide a detailed mechanism for the overall transformation. Provide a rationalization for the stereochemical outcome of the addition reaction. Three-dimensional drawings that illustrate chirality transfer should be provided.

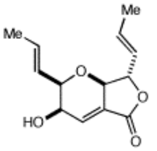


## Problem 497

Contributer: **Jon Scheerer**
Citation: *Organic Lett.* **2003**, *5*, 451
Keywords: Addition

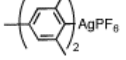
During the synthesis of the anti-tumor agent Waol A, Snider (*Org. Lett.* **2003**; 5(4); 451-454) and coworkers prepared the diastereomeric aldol adducts **A** and **B**. These substrates underwent iodoetherification at vastly different rates. In fact, to achieve sufficient conversion a more reactive iodonium reagent (bis(sym-collididne) $AgPF_6$) was necessary. *Please provide a mechanism for the reactions (**A** to **A'** and **B** to **B'**) that accounts for the observed selectivity and difference in rate. 3-dimensional representations are required.*





Waol A (FD-211)

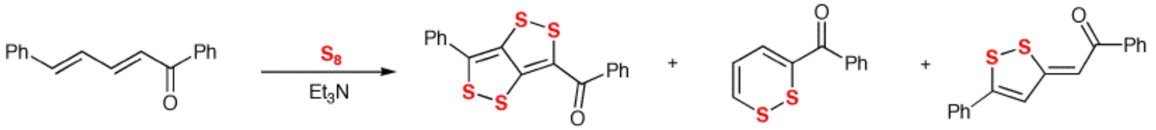
Conditions:
a) $I_2$, $NaHCO_3$ = 5% conv
b) $I_2$ = 88% yield



## Problem 581

Contributer: **Ben Hafensteiner**
Citation: *Heterocycles* **1993**, *36*, 223-229
Keywords: Addition

Sulfur oddities have intrigued chemists from the time the odiferous yellow compound was discovered. Here is problem derived from an investigation into elemental sulfur chemistry by the Purello group of the Universitá di Cantania (*Heterocycles*, **1993**, *36*, 223-229).

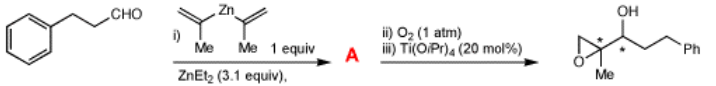


Provide one or more plausible mechanisms for this transformation identifiying all intermediates. Also, identify the active sulfur reagent in the above process.

## Problem 628

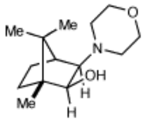
Contributer: **Jon Scheerer**
Citation: *J. Am. Chem. Soc.* **2004**, *126*, 13608
Keywords: Addition

A one-pot procedure for the enantioselective addition / diastereoselective epoxidation was recently developed in the laboratories of Patrick Walsh (*JACS*, **2004**, *126*, 13608.). This methodology can directly prepare up to 3 contiguous stereocenters. Please provide a mechanism for this transformation and predict the stereochemistry of the product. Your anwser should use 3-D representations and highlight intermediate **A**. *(Hint: oxygen is known to insert into organozinc species, forming zinc peroxides and titanium can transmetallate with zinc. The organometallic aspects of this question may be de-emphasized in your answer.)*



90% yield
85% ee

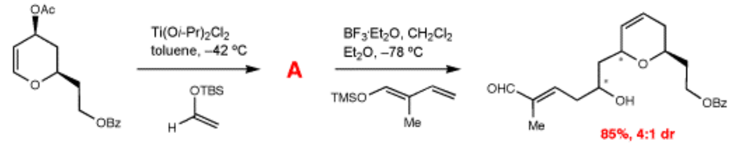
(–)-MIB



## Problem 630

Contributer: **Emily Balskus**
Citation: *Tetrahedron* **1995**, *51*, 9413
Keywords: Addition

The Paterson group used the following reaction sequence in a synthesis of swinholide A (*Tetrahedron*, **1995**, *51*, 9413):


OAc
O
OBz
$Ti(O\textit{i}\text{-}Pr)_2Cl_2$
toluene, –42 °C
OTBS
H
A
$BF_3{\cdot}Et_2O$, $CH_2Cl_2$
$Et_2O$, –78 °C
TMSO
Me
OHC
Me
OH
O
OBz
*

85%, 4:1 dr

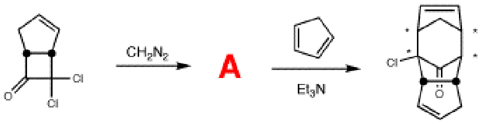
**Part A.** Provide the structure of intermediate **A** and the mechanism for its formation. Predict and account for the stereochemistry of **A** in your mechanism. Include 3-D drawings when relevant.

**Part B.** Provide a mechanism for the formation of the final product from intermediate **A**. Predict and account for the stereochemistry of the product in your mechanism. Include 3-D drawings when relevant.

## Problem 631

Contributer: **Jon Lawrence**
Citation: *Organic Lett.* **2001**, *36*, 2533
Keywords: Addition

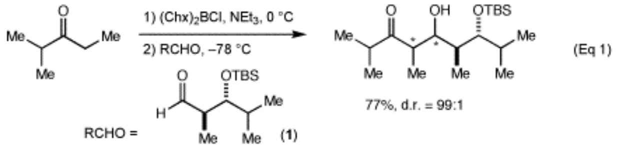
Harmata and co-workers reported the following interesting transformation (*Org. Lett.* **2001**, *3*, 2533.) Please provide a mechanism using 3-D representations where appropriate. Please identify intermediate **A** and assign the relative stereochemistry of the product.



## Problem 696

Contributer: **David A. Evans**
Citation:
Keywords: Addition

In the Ph.D. thesis of Dart (Harvard Univ. 1995), a systematic study of double stereodiffentiating aldol reactions was undertaken. The anti-configured chiral aldehyde (**1**) showed impressive selectivity (d.r. = 99 : 1) for the aldol addition of the dicyclohexyl boron enolate derived from ethyl isopropyl ketone (Eq 1).

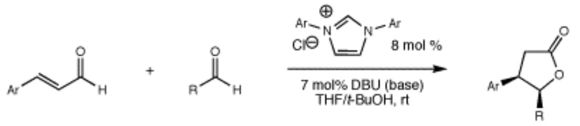


Please predict the major diasteromer and provide a rationale for the selectivity. Use of 3-D drawings is required.

## Problem 697

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2004**, *126*, 14379
Keywords: Addition

Bode and co-workers recently reported a new method for forming γ–butyrolactones from α,β-unsaturated aldehydes in the presence of catalytic amounts of bisarylimidazolium salts and base (*JACS*, **2004**, *126*, 14379).

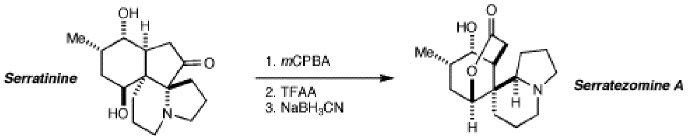


Propose a mechanism for this transformation that accounts for the use of catalytic amounts of salt . You do not need to explain the observed product stereochemistry in your answer.

## Problem 700

Contributer: **Jon Scheerer**
Citation: *J. Org. Chem.* **2002**, *67*, 5378
Keywords: Addition

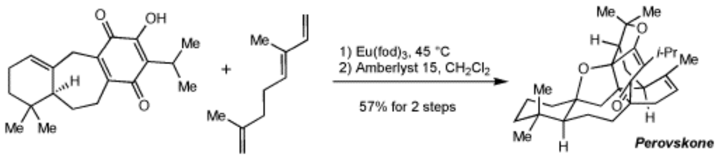
The following transformation of serratinine into serratezomine A was recently carried out in the laboratory to support the postulated biosynthesis of the *Lycopodium* alkaloid (*JOC*, **2002**, 67, 5378). Please provide a mechanism for the reaction.



## Problem 702

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1994**, *116*, 4979
Keywords: Addition

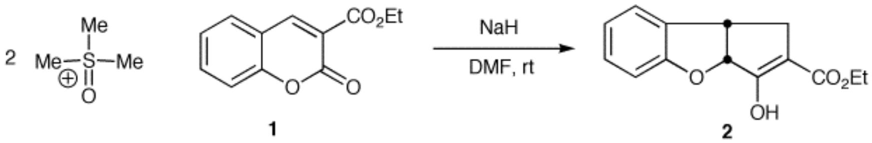
An elegant synthesis of the terpene perovskone has been reported (Majetich, *JACS*. **1994**, *116*, 4979.). Please provide a mechanism for this transformation making sure to explain relevant transition states with 3-D illustrations.
*(nb: Eu (Europium) is functioning as a Lewis acid catalyst; Amberlyst-15 is a mineral protic acid)*



## Problem 716

Contributer: **Michael DeMartino**
Citation: *Organic Lett.* **2001**, *3*, 1359
Keywords: Addition

During the course of studying the regioselectivity of cyclopropanecarboxylate ring openings, Ohta and coworkers discovered the transformation illustrated below (*Tetrahedron Letters* **1995**, *36*, 5603). When coumarin **1** was treated with excess (2.4 eq) of the Corey-Chaykovsky ylide, an unexpected product **2** was generated in 64 %. This new reaction has been applied to the first total synthesis of (±)-linderol A (*Org. Lett.* **2001**, *3*, 1359).



Provide a plausible mechanism for this transformation. The authors provide two different mechanisms (one in each of the aforementioned references), but did not attempt to prove either.

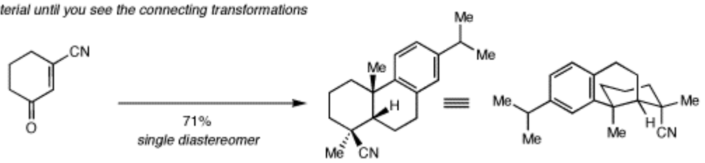
## Problem 729

Contributer: **Jon Scheerer**
Citation: *Angew. Chem.* **2004**, *43*, 1126
Keywords: Addition

The following multi-component, one-pot reaction was recently reported by Fleming (*Angew. Chem. Int. Ed.* **2004**, *43*, 1126.). This is an impressive reaction for two specific reasons: 1), only a single diastereomer is observed; 2), the reaction appears to be general for an array of Grignard reagents and electrophiles.

*Please provide a mechanism for the reaction that clearly explains the stereoselectivity for each step.*

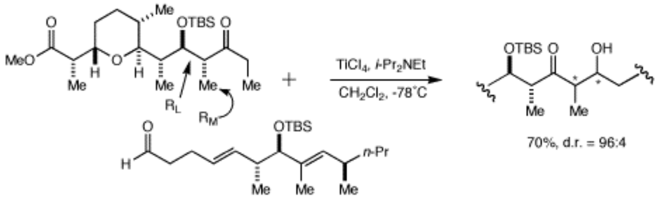
*Please use 3-D representations. I recommend working on this problem bi-directionally from both product and starting material until you see the connecting transformations*



## Problem 730

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2003**, 4037
Keywords: Addition

In a recent total synthesis of Zincophorin methyl ester (*Org. Lett.* **2003**, 4037), the following titanium-mediated aldol reaction was used to efficiently couple two large fragments. Predict the stereochemistry of the product and provide a stereochemical model to support your prediction.

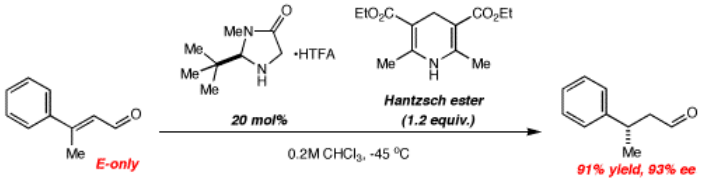


## Problem 734

Contributer: **Regan Thomson**
Citation: *J. Am. Chem. Soc.* **2005**, *127*, 32-33
Keywords: Addition

MacMillan and coworkers have recently reported the following enantioselective organo catalytic reduction of α,β-unsaturated aldehydes using a chiral iminium catalyst and the Hantzsch ester as the stoichiometric hydride source (*JACS*, **2005**, *127*, 32-33.).

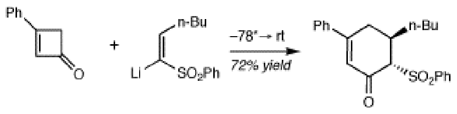
*Please provide a detailed reaction mechanism for this reduction and rationalize the observed sense of absolute stereochemical induction.*



## Problem 736

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2004**, *126*, 16265
Keywords: Addition

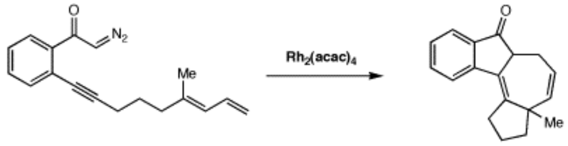
Please provide a mechanism for the following transformation recently reported by Magomedov and co-workers (*JACS* **2004**, 126, 16265) This is one of seven cases reported. *Be sure to classify any pericyclic processes that intervene.*



## Problem 741

Contributer: **Jon Scheerer**
Citation: *J. Org. Chem.* **1991**, *56*, 2523
Keywords: Addition

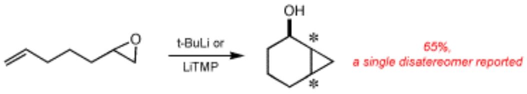
Please provide a mechanism for the following transformation (*JOC*, **1991**, *56*, 2523).



## Problem 761

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2004**, *126*, 8664
Keywords: Addition

Hodgson and so-workers recently reported the highly diastereoselective cyclopropanation illustrated below (*JACS*, **2004**, *126*, 8664). This intramolecular cyclopropanation appears to be general for five- as well as six-membered ring fomation.



65%, *a single disatereomer reported*

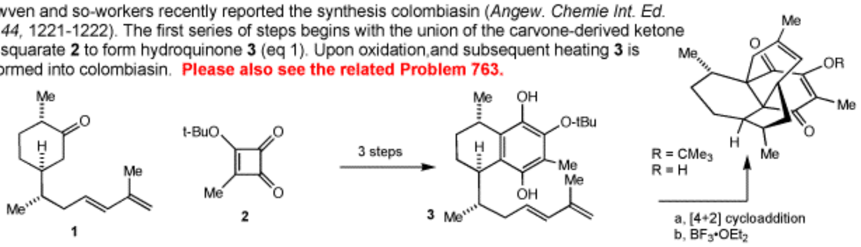
**(Part A).** Provide an FMO analysis of a generic carbene-olefin addition. Make sure that the orientation of the carbenoid relative to the olefin is clearly represented.

**(Part B).** Based on the transition geometry defined by the stereoelectreonic effects illlustrated in **Part A**, predict the product stereochemistry. Illustrate, with 3-dimensional representations the transition state for this reaction and justify your prediction. No credit will be given for an unjustified answer.

## Problem 762

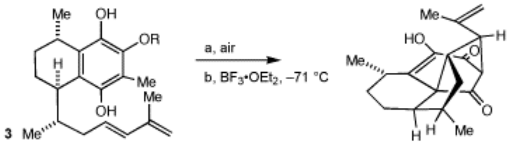
Contributer: **David A. Evans**
Citation: *Angew. Chem.* **2005**, *44*, 1221-1222
Keywords: Addition

Harrowven and so-workers recently reported the synthesis colombiasin (*Angew. Chemie Int. Ed.* **2005**, *44*, 1221-1222). The first series of steps begins with the union of the carvone-derived ketone **1** and squarate **2** to form hydroquinone **3** (eq 1). Upon oxidation,and subsequent heating **3** is transformed into colombiasin. **Please also see the related Problem 763.**



**Problem 762.** Using your general knowledge of organic chemistry, illustate the reactions and reagents needed to transform **1** and **2** into **3**. Please provide reasonable mechanisms for each of the steps

**Problem 763.** In an earlier study, Rychnovsky and co-workers demonstrated that structures related to **3** (R = Me) could be transformed innto the biogenetically related natural product elisapterosin (**4**) by treatment with $BF_3$•$OEt_2$ (*Angew. Chemie Int. Ed.* **2003**, *42*, 1267-1270).



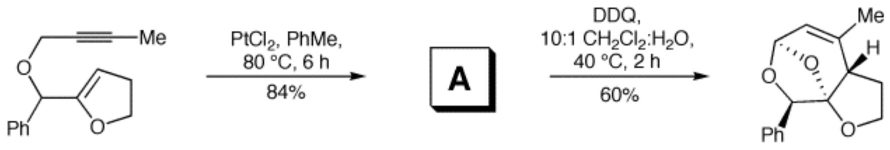
Elisapterosin (**4**)

Provide a mechanism for this transformation.

## Problem 765

Contributer: **Ryan Shenvi**
Citation: *Organic Lett.* **2004**, *6*, 3191
Keywords: Addition

Based on the pioneering work of Murai (*Organometallics* **1996**, *15*, 901) and Fürstner (*J. Am. Chem. Soc.* **2000**, *122*, 6785-6786), Echavarren and co-workers (*Org. Lett.* **2004,** *6*, 3191) demonstrated the interesting sequence of transformations shown below.

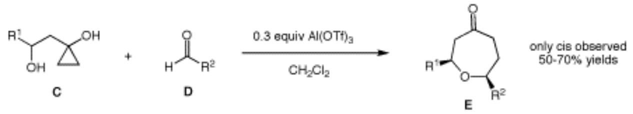

Me
O
Ph
O
PtCl$_2$, PhMe, 80 °C, 6 h
84%
A
DDQ, 10:1 CH$_2$Cl$_2$:H$_2$O, 40 °C, 2 h
60%
Me
H
O
O
Ph
O

Please show the correct structure of compound **A** and delineate a mechanism for each transformation.

## Problem 767

Contributer: **Karl Scheidt**
Citation: *Organic Lett.* **2005**, *7*, 515
Keywords: Addition

Ring expansions can drive reactions to provide interesting products. In recent work by Minbiole and coworkers (*Org. Lett.* **2005**, *7*, 515), the combination of cyclopropane alcohol **C** and aldehydes **D** affords the seven membered rings (**E**) with catalytic quantities of Lewis acids. Provide a mechanism for this process that accounts for the observed cis-diastereoselectivity.



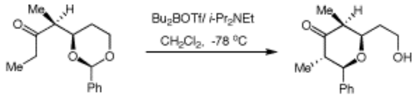
Your Answer:

## Problem 770

Contributer: **Karl Scheidt**
Citation: *Organic Lett.* **2004**, *6*, 123
Keywords: Addition

Please provide a rationale for the stereoselective synthesis of cyclic ethers in a single step shown by Sinha and coworkers (*Org. Lett.* **2004**, *6*, 123). Be sure to provide clear 3D drawing to account for the observed stereoselectivity. (Note: An excess of Bu$_2$BOTf (> 2 equiv) is necessary for the reaction to proceed.)

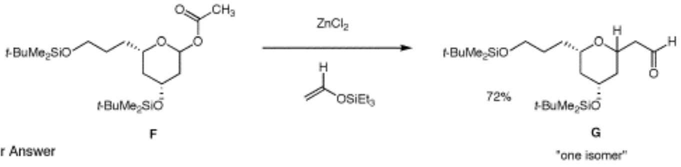
Your Answer:



## Problem 772

Contributer: **Karl Scheidt**
Citation: *J. Am. Chem. Soc.* **2001**, *123*, 10942
Keywords: Addition

In Amos Smith's synthesis of the natural product, phorboxazole, (*J. Am. Chem. Soc.* **2001**, *123*, 10942) the following acetate **F** was treated with ZnCl$_2$ and an enolsilane to afford pyran **G**. Provide a mechanism for this reaction and indicate what is the predominant diastereomer by providing a detailed depiction of the transition state. Assume an aqueous workup of the reaction.

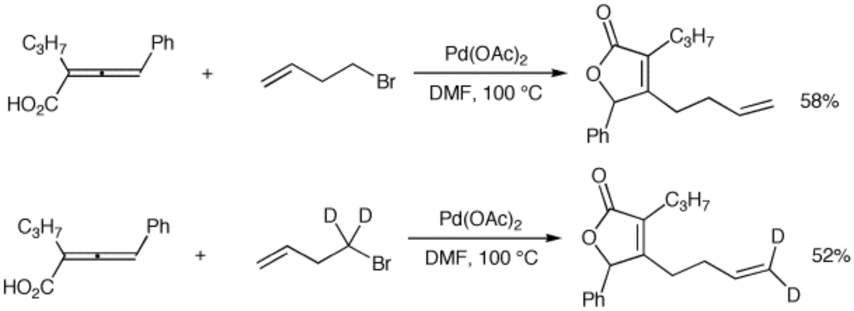


Your Answer

## Problem 775

Contributer: **Ryan Ashok Shenvi**
Citation: *Angew. Chem.* **2003**, *42*, 1955
Keywords: Addition

In a study of the Pd-mediated coupling reaction of 2,3-allenoic acids with ω-1-alkenyl halides, compound **1** was formed as the major product in 58% yield (*Angew. Chem. Int. Ed.*, **2003**, *42*, 1955). When the deuterium labeled substrate **2** was subjected to the same reaction conditions, product **3** was obtained in 52% yield.

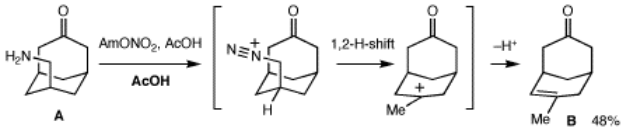


Propose a reasonable mechanism for the transformation that explains the fate of the deuterium atoms.

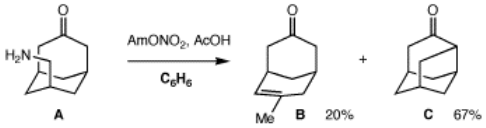
## Problem 784

Contributer: **Ian Fleming**
Citation: *J. Org. Chem.* **1973**, *38*, 3462
Keywords: Addition

Primary amines on treatment with nitrous acid give diazonium ions. These reactive intermediates are only isolated when the amine is aromatic. With aliphatic amines, the diazonium ion is a reactive intermediate which usually undergoes elimination or substitution reactions, sometimes preceded by cationic rearrangement. This was the result with the primary amine **A** when the reaction was carried out in acidic solution: the unsaturated ketone **B** was the major product (J.-H. Liu and P. Kovacic, *J. Org. Chem.*, 1973, **38**, 3462).



However, Liu and Kovacic found that, when the amount of acid was limited to one molar equivalent, the major product was the saturated ketone **C**.

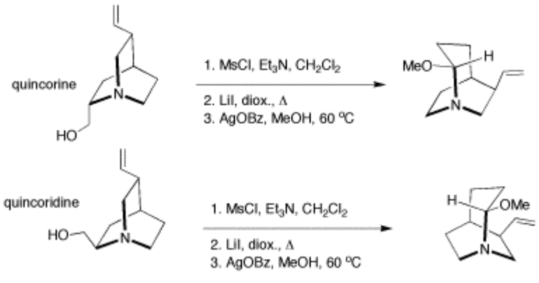


Account for the formation of the ketone **C**.

## Problem 786

Contributer: **Robert M. Williams**
Citation: *Organic Lett.* **2000**, *2*, 1661
Keywords: Addition

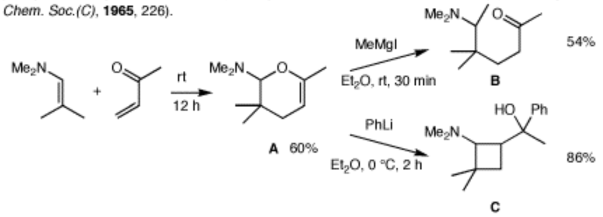
Hoffman, et al., reported the interesting ring expansion reaction of azabicyclo[2.2.2]octanes as shown below. Please provide a mechanistic rationalization for this transformation. Note that complete stereospecificity is observed from the two diastereomers quincorine and quincoridine; your mechanism should account for the observed stereospecificity.
(Roper, S.; Frackenpohl, J.; Schrake, O.; Wartchow, R.; Hoffmann, M.R., *Org. Lett.* **2000**, *2*, 1661; Roper, S.; Wartchow, R.; Hoffmann, M.R., *Org. Lett.* **2002**, *4*, 3179)



## Problem 789

Contributer: **Ian Fleming**
Citation: *J. Chem Soc (C)* **1965**, 226
Keywords: Addition

The *N,N*-dimethylenamine of isobutyraldehyde and methyl vinyl ketone react to give the dihydropyran **A**. When this compound was treated with methylmagnesium iodide, it gave the ketone **B**, but, when it was treated with phenyllithium, it gave the alcohol **C** (actually a mixture of two diastereoisomers) (I. Fleming and M. H. Karger, *J. Chem. Soc.(C)*, **1965**, 226).

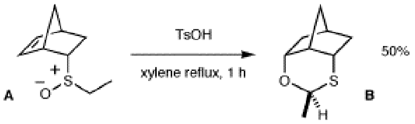


What are the pathways to these compounds, and explain how a ketone can be the product of a Grignard reaction?

## Problem 790

Contributer: **Ian Fleming**
Citation: *Chem. Commun.* **1995**, 1197
Keywords: Addition

The sulfoxide **A** isomerizes to the mixed acetal **B** on treatment with acid (H. Abe, J. Itani, C. Masunari, S. Kashino and T. Harayama, *Chem. Commun.*, **1995**, 1197).

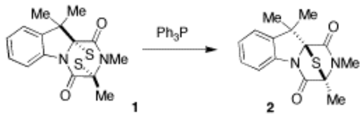


Explain this result.

## Problem 791

Contributer: **Robert M. Williams**
Citation: *J. Chem Soc (C)* **1971**, 1189
Keywords: Addition

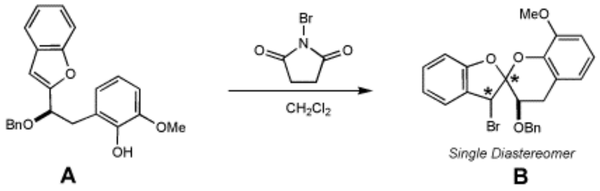
Safe and Taylor demonstrated with the aid of CD spectra that, phosphine-mediated desulfurization of the optically pure gliotoxin model epidithiapiperazinedione **1**, led to the epimonothiapiperazinedione (**2**) with the *opposite absolute configuration* to that of **1**. Provide a detailed mechanism that carefully accounts for the stereochemical inversion. (Safe, S.; Taylor, A. *J. Chem. Soc. (C)*, **1971**, 1189).



## Problem 801

Contributer: **Pavel Nagorny**
Citation: *Angew. Chem.* **2001**, *40*, 4709
Keywords: Addition

Danishefsky and coworkers reported that the *N*-bromosuccinimide-induced spiroketalization of benzofuran **A** affords the spiroketal **B** as a single diastereomer (*ACIEE*, **2001**,*40*, 4709).

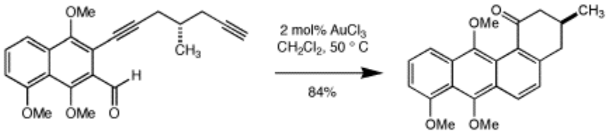


Using clear three-dimensional drawings provide a mechanism for this reaction and predict the stereochemistry of the product **B**. Be sure to indicate any important steric or stereoelectronic effects.

## Problem 805

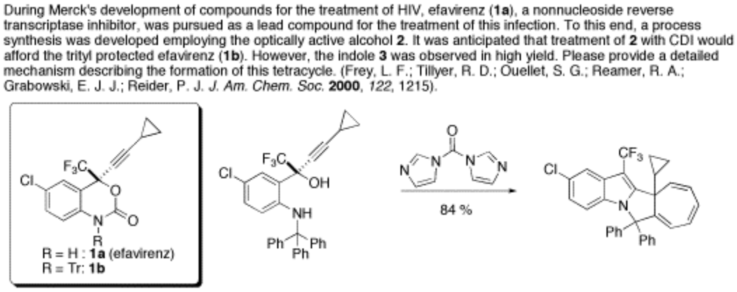
Contributer: **Karl Scheidt**
Citation: *J. Org. Chem.* **2005**, *70*, 8977
Keywords: Addition

This reaction below was employed by Sato, Asao and Yamamoto in the synthesis of the antibiotics (+)-rubiginone B2 and (+)-ochromycinone ( *J. Org. Chem.* **2005** ASAP). Provide a plausible mechanism for this reaction.



## Problem 806

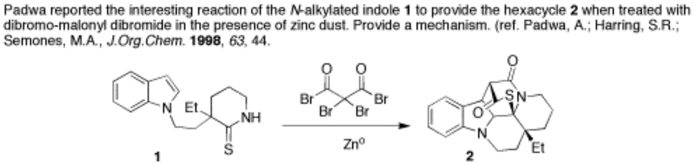
Contributer: **Robert M. Williams**
Citation: *J. Am. Chem. Soc.* **2000**, *122*, 1215
Keywords: Addition



During Merck's development of compounds for the treatment of HIV, efavirenz (**1a**), a nonnucleoside reverse transcriptase inhibitor, was pursued as a lead compound for the treatment of this infection. To this end, a process synthesis was developed employing the optically active alcohol **2**. It was anticipated that treatment of **2** with CDI would afford the trityl protected efavirenz (**1b**). However, the indole **3** was observed in high yield. Please provide a detailed mechanism describing the formation of this tetracycle. (Frey, L. F.; Tillyer, R. D.; Ouellet, S. G.; Reamer, R. A.; Grabowski, E. J. J.; Reider, P. J. *J. Am. Chem. Soc.* **2000**, *122*, 1215).

## Problem 807

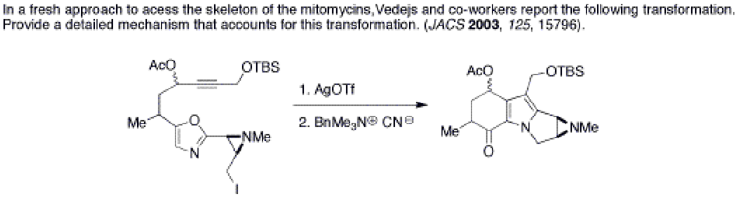
Contributer: **Robert M. Williams**
Citation: *J. Org. Chem.* **1998**, *63*, 44
Keywords: Addition



Padwa reported the interesting reaction of the *N*-alkylated indole **1** to provide the hexacycle **2** when treated with dibromo-malonyl dibromide in the presence of zinc dust. Provide a mechanism. (ref. Padwa, A.; Harring, S.R.; Semones, M.A., *J.Org.Chem.* **1998**, *63*, 44.

## Problem 808

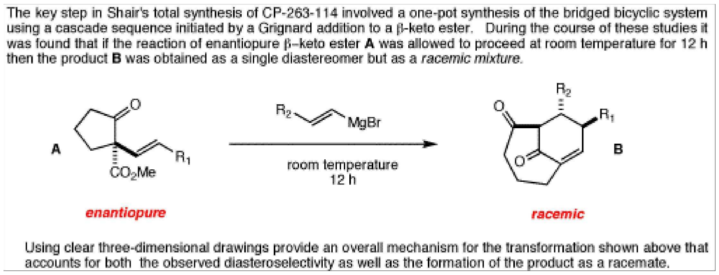
Contributer: **Robert M. Williams**
Citation: *J. Am. Chem. Soc.* **2003**, *125*, 15796
Keywords: Addition



In a fresh approach to acess the skeleton of the mitomycins,Vedejs and co-workers report the following transformation. Provide a detailed mechanism that accounts for this transformation. (*JACS* **2003**, *125*, 15796).

## Problem 813

Contributer: **Regan Thomson**
Citation: *Angew. Chem.* **2005**, *44*, 2259
Keywords: Addition

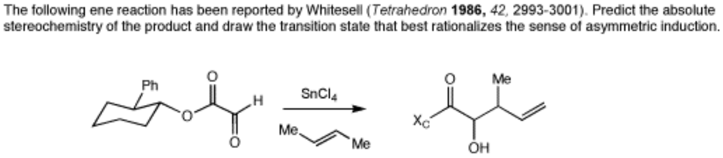


The key step in Shair's total synthesis of CP-263-114 involved a one-pot synthesis of the bridged bicyclic system using a cascade sequence initiated by a Grignard addition to a β-keto ester. During the course of these studies it was found that if the reaction of enantiopure β–keto ester **A** was allowed to proceed at room temperature for 12 h then the product **B** was obtained as a single diastereomer but as a *racemic mixture*.

Using clear three-dimensional drawings provide an overall mechanism for the transformation shown above that accounts for both the observed diasteroselectivity as well as the formation of the product as a racemate.

## Problem 818

Contributer: **David A. Evans**
Citation: *Tetrahedron* **1986**, *42*, 2993-3001
Keywords: Addition

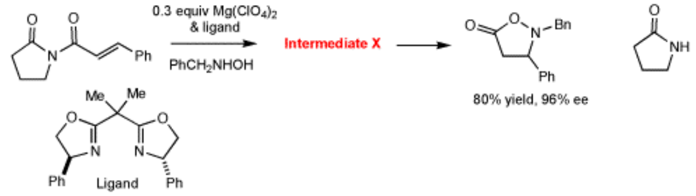


The following ene reaction has been reported by Whitesell (*Tetrahedron* **1986**, *42*, 2993-3001). Predict the absolute stereochemistry of the product and draw the transition state that best rationalizes the sense of asymmetric induction.

## Problem 819

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2000**, *21*, 3393-3396
Keywords: Addition

The following heteroconjugate addition reaction has been reported by Sibi( *Org Lett.* **2000**, *2*,3393-3396). Predict the absolute stereochemistry of the product and draw the transition state that best rationalizes the sense of asymmetric induction.

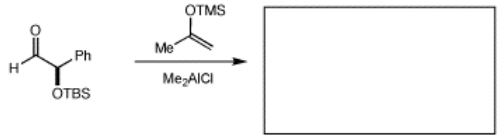


## Problem 820

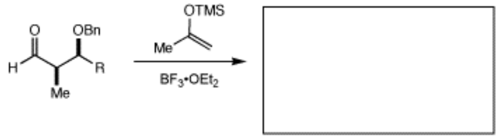
Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1996**, *118*, 4322
Keywords: Addition

Predict the stereochemical outcome for each of the illustrated transformations. Draw the major product diastereomer in the box provided.

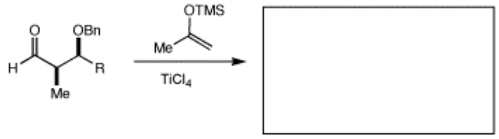
**Part A: (3 points)**



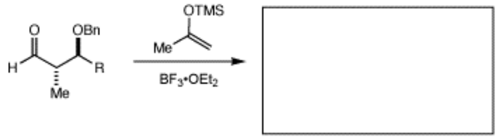
**Part B: (3 points)**



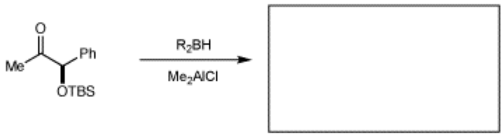
**Part C: (3 points)**



**Part D: (3 points)**



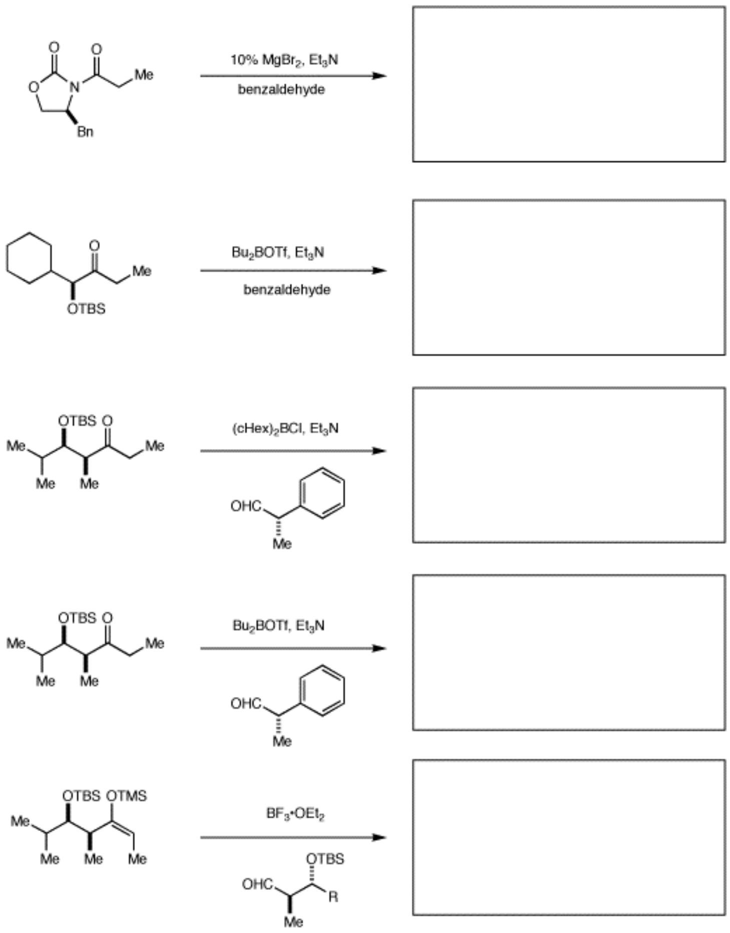
**Part E: (3 points)**



## Problem 823

Contributer: **Regan Thomson**
Citation:
Keywords: Addition

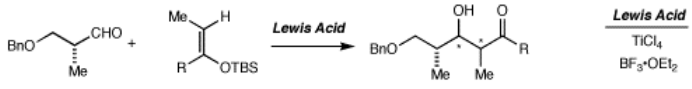
For each of the following aldol reactions provide the major product that you would expect to form under the given conditions. Provide the expected stereochemical outcome



## Problem 824

Contributer: **Regan Thomson**
Citation: *Tetrahedron* **1986**, *42*, 893
Keywords: Addition

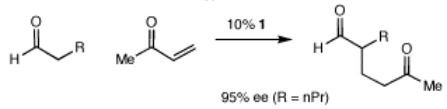
Using clear 3-dimensional transition state representations, predict the expected stereochemical outcome for the following Mukaiyama aldol reactions when using each of the two indicated Lewis acids.

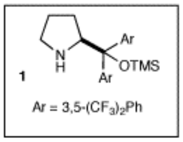


## Problem 826

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2005**, *127*, 18296-18304
Keywords: Addition

In a *JACS ASAP* article that recently appeared on the web, Jorgensen and co-workers have reported that amine **1** is an excellent catalyst for the enantioselective α-functionalization of aldehydes with electrophiles. In all instances, the sense of asymmetric induction is the same. A typical reaction is shown below:





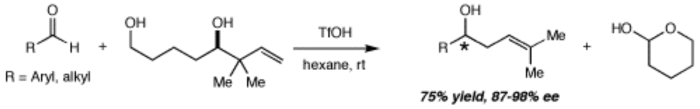
**Part A. (10 Points).** Precict the sense of asymmetric induction and provide a 3-dimensional drawing to support your prediction.

**Part B. (5 Points).** Explain why the iminium ion intermediate does not racemize under the reaction conditions. Illustrate your answer with a graphic.

## Problem 829

Contributer: **Regan Thomson**
Citation: *J. Am. Chem. Soc.* **2003**, *125*, 4990
Keywords: Addition

The prenyl group is an essential unit in the biosynthesis of terpene natural products. Due to the large number of natural products that contain this moiety, methods for its selective introduction into molecules are highly useful. Loh and Cheng have descibed a general regioselective and highly enantioselective prenylation of aldehydes, as shown below (*JACS* **2003**, *125*, 4990).

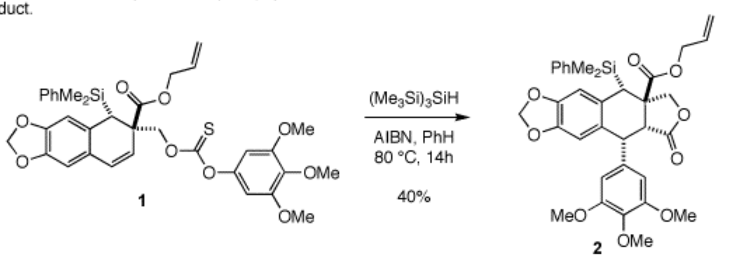


Please provide a general mechanism for this interesting reaction and using clear three-dimensional drawings predict the absolute stereochemical outcome.

## Problem 830

Contributer: **Mohammad Movassaghi**
Citation: *J. Am. Chem. Soc.* **2003**, *125*, 12108
Keywords: Addition

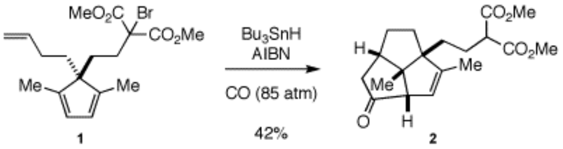
The conversion of thionocarbonate **1** to the lactone **2** was used as a key step in the preparation of an advanced intermediate toward the synthesis of podophyllotoxin (*JACS* **2003**, *125*, 12108). Provide a mechanism for the formation of the product.



## Problem 836

Contributer: **Mohammad Movassaghi**
Citation: *J. Chem. Soc. Perkin Trans 1* **1998**, 1591
Keywords: Addition

During stuides directed toward the synthesis of crinipellin A, curran reported an interesting carbonylative tandem radical cyclization (*JCS, PT 1*, **1998**, 1591). Provide a mechanism for the conversion of triene **1** to tricycle **2**.

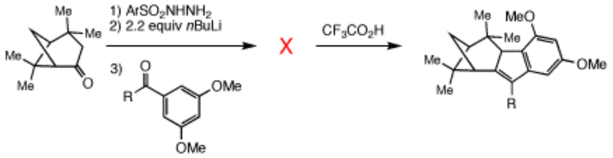


***ANSWER:***

## Problem 838

Contributer: **Keith Fandrick**
Citation: *Organometallics* **2002**, 144
Keywords: Addition

Rupert published the following transformation in his effort towards the synthesis of the Verbeninidenes (*Organometallics* **2002**, 144).

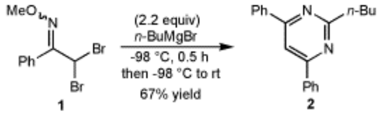


In the space below please provide a reasonable mechanism for the transformations outlined above. Be sure to clearly identify **X**.

## Problem 844

Contributer: **Dennie Welch**
Citation: *J. Am. Chem. Soc.* **2002**, *124*, 9032
Keywords: Addition

The construction of pyrimidine cores from α,α-dibromo oxime ethers was reported by workers in Japan (*J. Am. Chem. Soc.* **2002**, *124*, 9032-3). Please provide a mechanism for the reaction below (**1** to **2**) and account for the stoichiometry of Grignard reagent employed to effect the transformation.

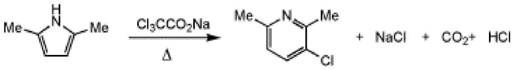


**Answer:**

## Problem 847

Contributer: **Keith Fanfrick**
Citation:
Keywords: Addition

The following reaction was reported for the synthesis of substituted pyridines as shown below. Provide a reasonable mechanism for the transformation. Identify and describe any pericyclic processes that might be involved(Thomas L. Gilchrist, *Heterocyclic Chemistry*. 3rd Ed. Longman Press: England, **1997**).

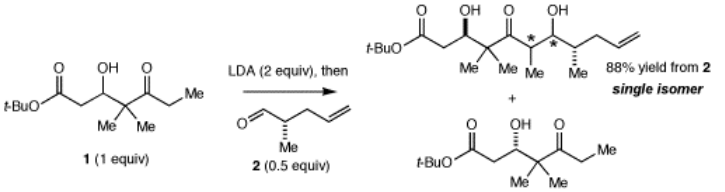


**Your Answer:**

## Problem 850

Contributer: **Pavel Nagorny**
Citation:
Keywords: Addition

During the preparation of epothilone analogs, the following aldol reaction was investigated by Danishefsky and Zhang (Zhang, *PHD Dissertation*, **2003**). It was noted that if only 0.5 equivalents of the enantiopure aldehyde **2** was used then effective kinetic resolution of the racemic ketone **1** was achieved (*ie* only one enantiomer of the enolate reacts).

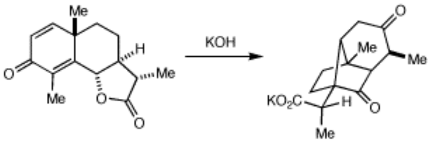


Using clear three dimensional representations please provide a rationale for the observed resolution and predict the relative stereochemistry of the aldol adduct (***HINT:*** The enolate is likely to be chelated with the beta-alkoxy substituent).

## Problem 851

Contributer: **Regan Thomson**
Citation: *J. Am. Chem. Soc.* **1948**, *70*, 4216
Keywords: Addition

Woodward and coworkers reported the following base-promoted conversion of α-santonin into potassium santanoate as part of a classic natural product structural determination (*JACS* **1948**, *70*, 4216). In the space below please provide a concise mechanism for this intriguing rearrangement.
*Hint: Work on the analysis of this transformation bi-directionally.*

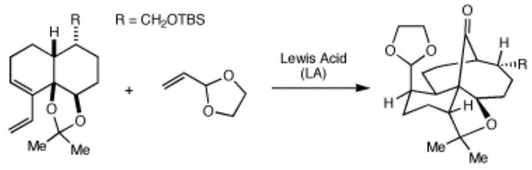


**Your Answer:**

## Problem 856

Contributer: **Meredth McGowen**
Citation: *Organic Lett.* **2005**, *7*, 5921
Keywords: Addition

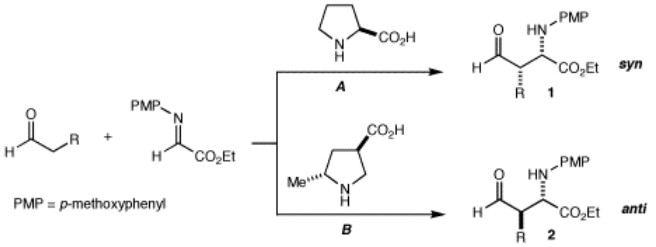
Barriault recently published the following Lewis-acid mediated reaction cascade as a strategy to rapidly assemble highly functionalized bicycloalkanones (*Org. Lett.* **2005**, *7*, 5921). Using clear 3D representations, please provide a mechanism that includes a rationalization for the relative stereochemistry observed in the product.



## Problem 859

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2006**, *128*, 1040
Keywords: Addition

The Mannich reaction catalyzed by proline (**A**) typically provides the **syn** adduct **1** with high levels of syn diastereocontrol. However, Barbas and coworkers have recently reported that catalyst **B** affords the corresponding **anti** adduct **2** with high selectivity (*JACS* **2006,** *128*, 1040).



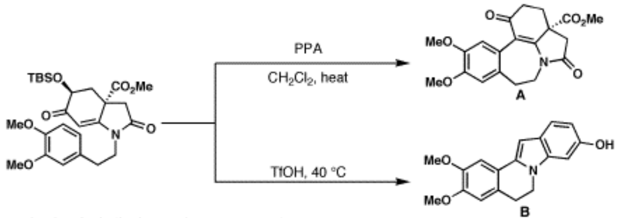
**Part A.** Please provide a clear depiction of the transition state leading to the formation of the observed syn adduct **1** when using **A**. Your answer should discuss the issues associated with the initially formed enamine intermediate, and identify all important control elements that determine enantio- and diastereoselectivity.

**Part B.** In contrast to above, please provide a clear depiction of the transition state leading to the formation of the observed anti product **2** when using **B**. Your answer should discuss the issues associated with the initially formed enamine intermediate and identify important control elements that determine enantio- and diastereoselectivity.

## Problem 861

Contributer: **David Lin**
Citation: *Organic Lett.* **2006**, *8*, 601-604
Keywords: Addition

While developing a route to the synthesis of Erythrina alkaloids, Padwa and colleagues encountered the following transformations (Org. Lett. **2006**, *8*, 601-604).

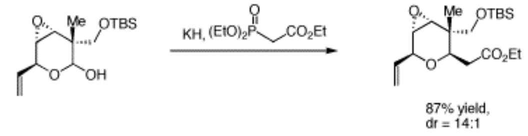


Propose a mechanism for both observed rearrangements.

## Problem 863

Contributer: **Karl Scheidt**
Citation: *Organic Lett.* **2006**, *88*, 475-478
Keywords: Addition

In Shishido's total synthesis of (+)-Lasonolide A (*Org. Lett.* **2006**, *8*, 475-478) the following step is reported. Please provide a mechanism and account for the diastereoselctivity.

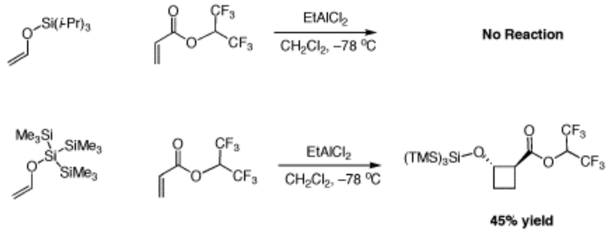


**Your answer**

## Problem 865

Contributer: **Karl Scheidt**
Citation: *Organic Lett.* **2005**, *71*, 3127-3129
Keywords: Addition

Yamamoto has reported the following sequence of reactions which proceed smoothly with the tris(trimethylsilyl)silyl enol ether but not with traditional TIPS or TBS groups (*Org. Lett.* **2005**, *7*, 3127-3129). Provide a rationale for these observations that *includes a detailed FMO analysis*. You do not have to explain the diastereoselectivity. HINT: This reaction is NOT a **concerted** [2+2] reaction.

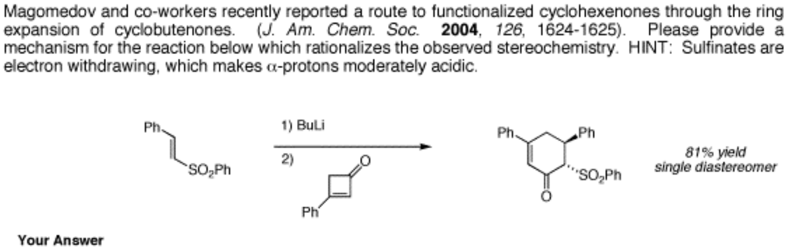


## Problem 867

Contributer: **Karl Scheidt**
Citation: *J. Am. Chem. Soc.* **1985**, *107*, 256-257
Keywords: Addition

## Problem 868

Contributer: **Karl Scheidt**
Citation: *J. Am. Chem. Soc.* **2004**, *126*, 1624-1625
Keywords: Addition



Magomedov and co-workers recently reported a route to functionalized cyclohexenones through the ring expansion of cyclobutenones. (*J. Am. Chem. Soc.* **2004**, *126*, 1624-1625). Please provide a mechanism for the reaction below which rationalizes the observed stereochemistry. HINT: Sulfinates are electron withdrawing, which makes $\alpha$-protons moderately acidic.

Ph
SO$_2$Ph
1) BuLi
2)
O
Ph
Ph
Ph
SO$_2$Ph
O

*81% yield*
*single diastereomer*

**Your Answer**

## Problem 869

Contributer: **Karl Scheidt**
Citation: *Angew. Chem.* **2005**, *44*, 3485-3488
Keywords: Addition

## Problem 872

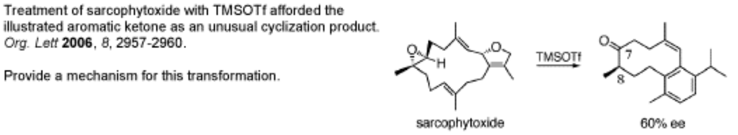
Contributer: **Jeremy Richter**
Citation: *J. Org. Chem.* **1993**, *58*, 5699-5701
Keywords: Addition

## Problem 873

Contributer: **Carlos Guerrero**
Citation: *Organic Lett.* **2003**, *5*, 333
Keywords: Addition

## Problem 874

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2006**, *88*, 2957-2960
Keywords: Addition

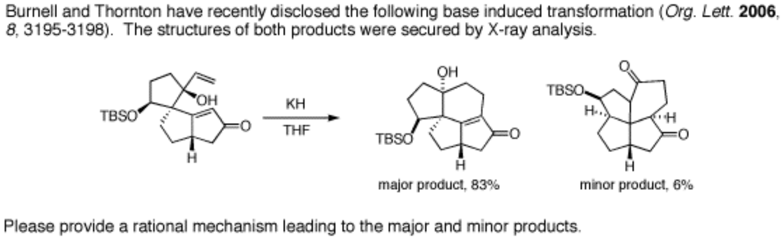


Treatment of sarcophytoxide with TMSOTf afforded the illustrated aromatic ketone as an unusual cyclization product. *Org. Lett* **2006**, *8*, 2957-2960.

Provide a mechanism for this transformation.

## Problem 875

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2006**, *88*, 3195-3198
Keywords: Addition



Burnell and Thornton have recently disclosed the following base induced transformation (*Org. Lett.* **2006**, *8*, 3195-3198). The structures of both products were secured by X-ray analysis.

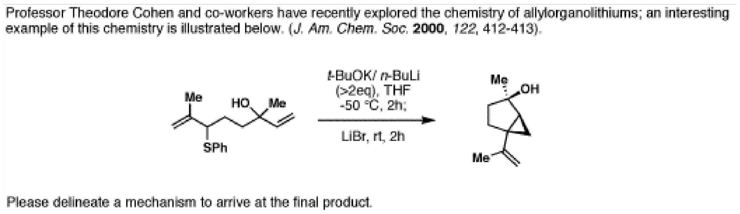
major product, 83%

minor product, 6%

Please provide a rational mechanism leading to the major and minor products.

## Problem 876

Contributer: **Ryan Shenvi**
Citation: *J. Am. Chem. Soc.* **2000**, *122*, 412-413
Keywords: Addition

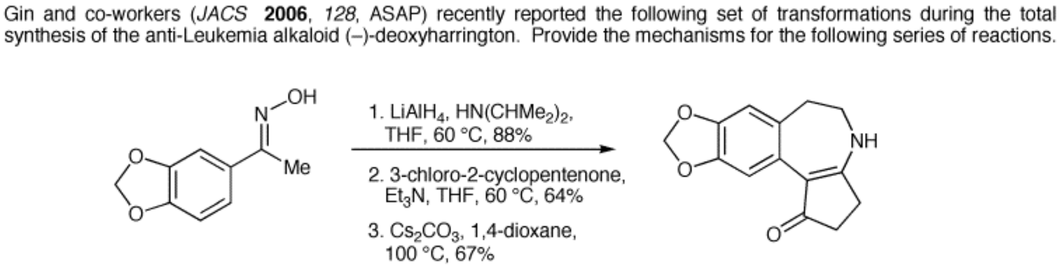


Professor Theodore Cohen and co-workers have recently explored the chemistry of allylorganolithiums; an interesting example of this chemistry is illustrated below. (*J. Am. Chem. Soc.* **2000**, *122*, 412-413).

Please delineate a mechanism to arrive at the final product.

## Problem 877

Contributer: **Karl Scheidt**
Citation: *J. Am. Chem. Soc.* **2006**, *128*, ASAP
Keywords: Addition



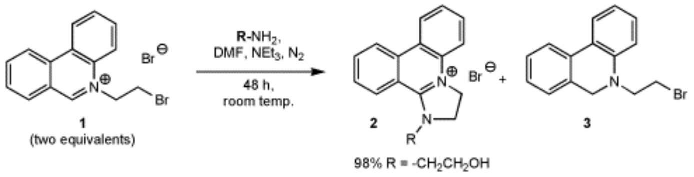
Gin and co-workers (*JACS* **2006**, *128*, ASAP) recently reported the following set of transformations during the total synthesis of the anti-Leukemia alkaloid (–)-deoxyharrington. Provide the mechanisms for the following series of reactions.

N
OH
O
O
Me
1. LiAlH4, HN(CHMe2)2, THF, 60 °C, 88%
2. 3-chloro-2-cyclopentenone, Et3N, THF, 60 °C, 64%
3. Cs2CO3, 1,4-dioxane, 100 °C, 67%
O
O
NH
O

## Problem 885

Contributer: **Christian Markert**
Citation: *J. Org. Chem.* **2004**, *69*, 8410
Keywords: Addition

The following reaction was found serendipitously by Cronin while attempting to functionalize the side chain of starting material **1** (JOC **2004**, *69*, 5934, see also Tetrahedron **2005**, *61*, 8410).

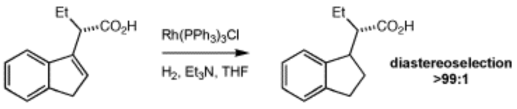


Provide a plausible mechanism for the indicated transformation. Your answer should include an explanation for the formation of **3** and a rationalization for the driving force for its formation.

## Problem 888

Contributer: **Pavel Nagorny**
Citation: *Organic Lett.* **2003**, *5*, 1587-1589
Keywords: Addition

Please predict the stereochemical outcome of the following reactions by *indicating the stereochemistry of the product.* Please use clear 3D drawings of the relevant conformations to explain your prediction.

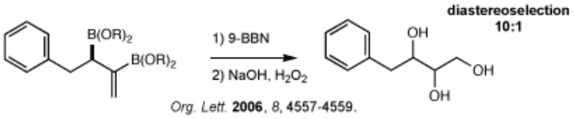


*Org. Lett.* **2003**, *5*, 1587-1589.

## Problem 889

Contributer: **Pavel Nagorny**
Citation: *Organic Lett.* **2006**, *88*, 4557-4559
Keywords: Addition

Please predict the stereochemical outcome of the following reaction by *indicating the stereochemistry of the product.* Please use clear 3D drawings of the relevant conformations to explain your prediction.

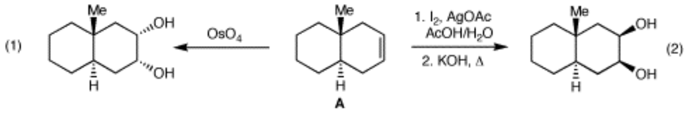


*Org. Lett.* **2006**, *8*, 4557-4559.

## Problem 891

Contributer: **David A. Evans**
Citation:
Keywords: Addition

If an olefin such as **A** experiences a facial bias, one may count on steric effects to direct the course of a OsO$_4$ dihydroxylation to the *less hindered olefin diastereoface* (eq 1). Strategically, it is limportant to be able access the other stereochemical option: dihydroxylation from the *more hindered olefin diastereoface*. This stereochemical option may be implemented through the reaction summarized in equation 2. This reaction has been referred to as the Prevost-Winstein-Woodward dihydroxylation.

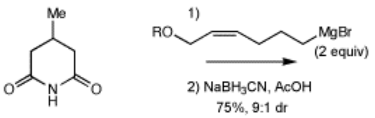


Provide a mechanism for the reaction illustrated in eq 2 in the space below. Since stereochemical issues are at stake, carefully rendered 3-D conformational drawings should be incorporated into your answer.

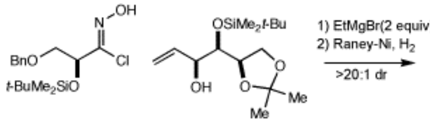
## Problem 898

Contributer: **Pavel Nagorny**
Citation:
Keywords: Addition

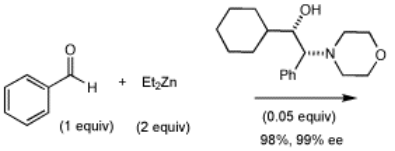
Predict the products for the transformations below. Also, provide mechanisms with the appropriate 3D models that explain your answer.



Gerasyuto, A. I.; Hsung, R. P. *Org.Lett.* **2006**, *8*, 4899-4902.



Burch, J. D. *Ph.D. Thesis*, Harvard University, **2005**.

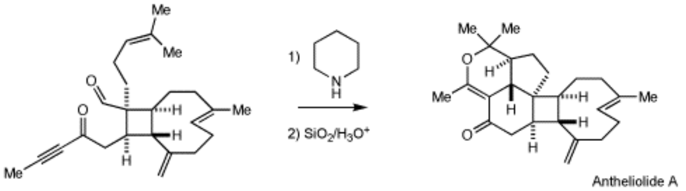


Nugent, W. A. *Org. Lett.* **2002**, *4*, 2133.

## Problem 900

Contributer: **Pavel Nagorny**
Citation: *J. Am. Chem. Soc.* **2006**, *128*, 14050
Keywords: Addition

Recently, the sequence of reactions outlined below was used by Corey et al. (*JACS* **2006**, *128*, 14050) in their route to antheliolide A. Provide a mechanism for this reaction and explain the stereochemistry of the product.

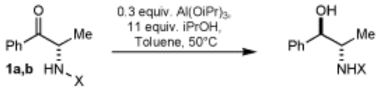


Antheliolide A

## Problem 903

Contributer: **Christian Markert**
Citation: *J. Org. Chem.* **2006**, *71*, 840
Keywords: Addition

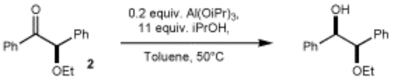
Merck Research Laboratoriesrecently reported the following preparation of ephedrine analogues (*JOC* **2006**, *71*, 840):



**1a**: X = BnO(C=O)-: dr > **99:1**
**1b**: X = *p*-MePhSO$_2$-: dr = 82:18

**Part A.** Explain the reactions of **1a-b** using clear 3D-drawings. Discuss the role of the nitrogen substituents. Note that **no racemization** was observed during the reaction!

**Part B.** Subjecting ether **2** to the same conditions, the *syn*-product was obtained with high selectivity. Provide a 3D transition state drawing that explains this selectivity.



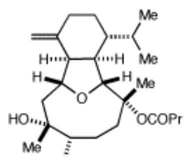
dr = 95.5:4.5

## Problem 905

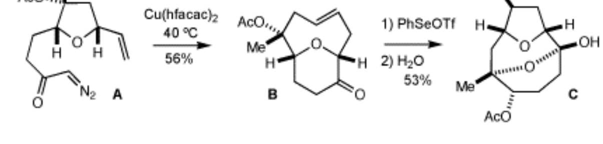
Contributer: **Pavel Nagorny**
Citation: *SynLett* **2006**, *14*, 2191
Keywords: Addition

In a recent report on studiesdirected toward the synthesis of the cladiellins (Clark *et al.* *Synlett* **2006**, *14*, 2191) the depicted transformations were used to construct the macrocycle of litophynin E.

Explain the formation of **B** from **A** and **C** from **B** by drawing a mechanism for these transformations.



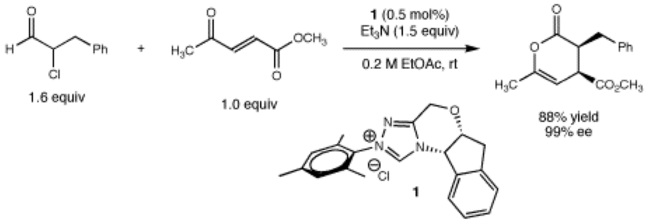
Litophynin E



## Problem 908

Contributer: **mathieu Lalonde**
Citation: *J. Am. Chem. Soc.* **2006**, *128*, 15088-15089
Keywords: Addition

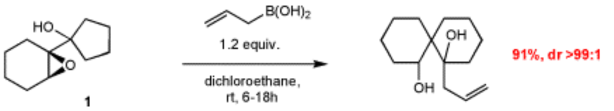
The transformation depicted below was recently reported by Bode and coworkers (*J. Am. Chem. Soc.* **2006**, *128*, 15088-15089.). Provide a mechanism for this transformation that accounts for the observed **relative** stereochemistry. **The absolute stereochemistry of the product does not need to be justified.**



## Problem 909

Contributer: **Christian Markert**
Citation: *Angew. Chem.* **2004**, *43*, 1702
Keywords: Addition

Tu *et al.* reported the following useful construcion that could be used for a diastereoselective generation of the illustrated bicyclic structures with quarternary stereocenters. (*ACIEE* **2004**, *43*, 1702).

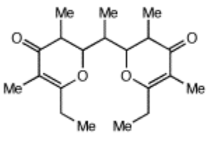


Please predict stereochemistry of the product and provide a mechanism that would support your predictions.

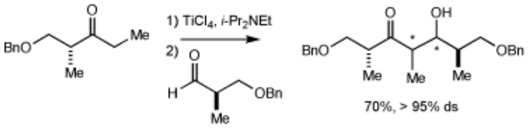
## Problem 910

Contributer: **Pavel Nagorny**
Citation: *Organic Lett.* **2001**, *34*, 123-126
Keywords: Addition

The illustrated below aldol addition reaction was used to construct the core of natural product (–)-memberone-C (Perkins, M. V.; Sampson, R. A. *Org. Lett.* **2001**, *3*, 123-126). Provide the stereochemistry of the product and show the transition state of this reaction with clear 3D drawings.



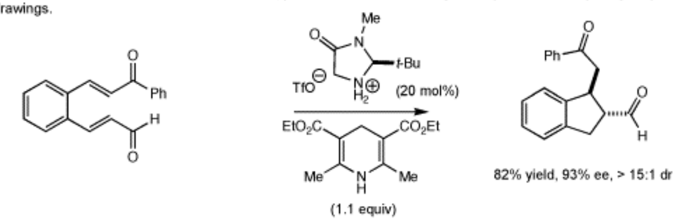
memberone-C



## Problem 911

Contributer: **Pavel Nagorny**
Citation: *J. Am. Chem. Soc.* **2005**, *127*, 15036-15037
Keywords: Addition

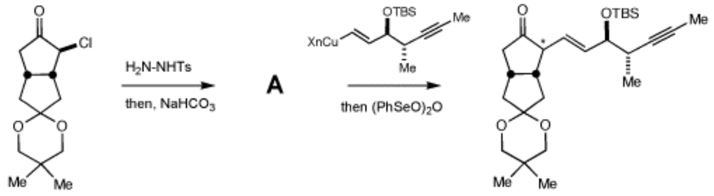
The following tandem process was recently reported by the List group (*J. Am. Chem. Soc.* **2005**, *127*, 15036-15037). Please provide the mechanism for this transformation, predict the stereochemistry of the product and explain your predictions with clear 3D drawings.



## Problem 912

Contributer: **Pavel Nagorny**
Citation: *J. Am. Chem. Soc.* **2005**, *ASAP*,
Keywords: Addition

The following sequence has recently been developed during the synthesis of Prostacyclin (Gais et al. *JACS*. **2005**, *ASAP*).

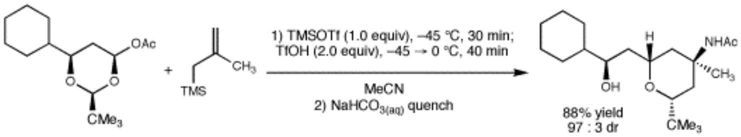


Please provide the structure of compound A, stereochemistry of the product and the mechanism of the transformations above. Explain the role of $(PhSeO)_2O$. *You do not need to provide the mechanism for this step.*

## Problem 913

Contributer: **Mathieu Lalonde**
Citation: *J. Am. Chem. Soc.* **2006**, *ASAP*,
Keywords: Addition

The transformation depicted below was recently reported by Rovis and coworkers (Epstein, O. L.; Rovis, T. *J. Am. Chem. Soc.* **2006**, ASAP). Provide a mechanism for this transformation that accounts for the observed diastereoselectivity.

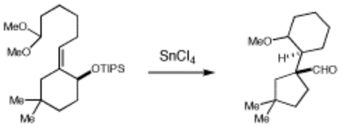


OAc
O
O
CMe3
+
CH3
TMS
1) TMSOTf (1.0 equiv), –45 °C, 30 min;
TfOH (2.0 equiv), –45 → 0 °C, 40 min
MeCN
2) NaHCO3(aq) quench
H
NHAc
CH3
OH
O
CMe3
88% yield
97 : 3 dr

## Problem 915

Contributer: **Karl Scheidt**
Citation: *J. Org. Chem.* **2006**, *71*, 1581-1587
Keywords: Addition

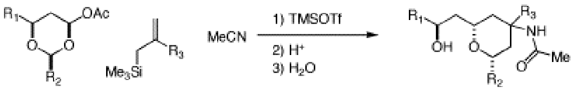
Overman has been a major contributor in the field of carbocation chemistry. In 2006, he observed that the following reaction proceeded with complete retention of absolute configuration (*J. Org. Chem.* **2006**, *71*, 1581-1587). Please provide a mechanism for this transformation which includes 3-dimensional structures and a rationale for the stereochemical outcome. Be sure to label all pericyclic processes.



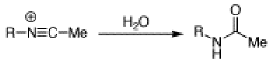
## Problem 920

Contributer: **Karl Scheidt**
Citation: *J. Am. Chem. Soc.* **2006**, *128*, 16480-16481
Keywords: Addition

Rovis and co-workers (*JACS* **2006**, *128*, 16480-16481) reported the following one-pot transformation which proceeds with good yield and excellent diastereoselectivity. Please provide a detailed mechanism for this reaction with 3-dimensional structures that provide a rationale for the observed selectivity. Be sure to classify all pericyclic reactions.



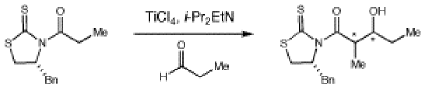
**HINT:**



## Problem 921

Contributer: **Karl Scheidt**
Citation: *Organic Lett.* **2006**, *81*, 2191-2194
Keywords: Addition

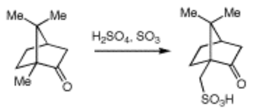
In 2006, Crimmins completed a total synthesis of 6-deoxyerythronolide B (*Org. Lett.* **2006**, *8*, 2191-2194). His first step was the reaction shown below. The two stereogenic centers he installs with this transformation allow him to use substrate control to set the remaining stereogenic centers in the molecule. Please predict the product and provide a rationale for this reaction using 3-dimensional structures.



## Problem 922

Contributer: **Karl Scheidt**
Citation:
Keywords: Addition

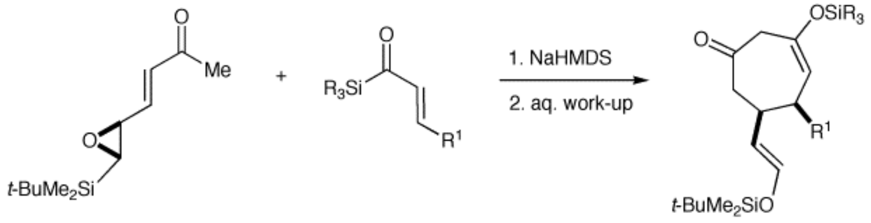
Camphor is prone to rearrangement when exposed to acid. Camphorsulfonic acid (CSA), which is a common reagent in organic synthesis, is formed when camphor is treated sulfuric acid and sulfur trioxide. Please provide a mechanism using 3-dimensional structures.



### Problem 923

Contributer: **Karl Scheidt**
Citation: *J. Org. Chem.* **2007**, *72*, 1379
Keywords: Addition

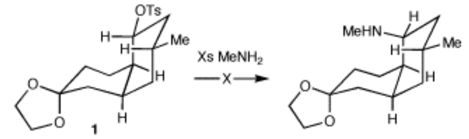
Takeda and coworkers recently reported the following formal [3+4] addition for the synthesis of 7-membered ketones (*J. Org. Chem.* **2007**, *72*, 1379). Please provide a mechansim for the generation of the product.



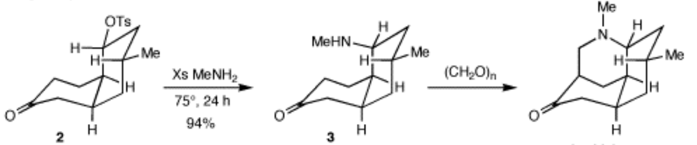
### Problem 924

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1972**, *94*, 4780
Keywords: Addition

In Evans' reported synthesis of lucidulene (*JACS* **1972**, *94*, 4780) the intractable substitution reaction illustrated below was encountered. This result was not surprising since the sterically conjested concave face of the cis decalin ring system would certainly disfavor substitution.It is also well known that cyclohexyl tosylates are prone to undergo elimination in addition to substitution with amine nucleophiles.



In liu of the problems encountered in the execution of this transformation, it is of interest to note that the desired transformation of **2** to **3** was achieved in 94% yield. From this advanced intermediate, the synthesis was completed in a single step.



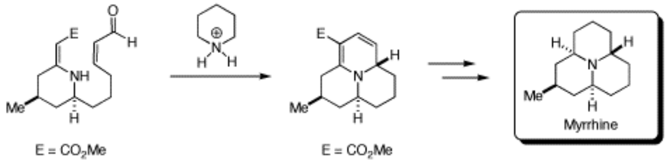
Lucidulene

Please provide an explanation for why amine substitution with tosylate **2** was successful while the analogous reaction on tosylate **1** was not.

### Problem 928

Contributer: **Karl Scheidt**
Citation: *J. Org. Chem.* **2007**, *72*, 2476-2484
Keywords: Addition

In Hsung's synthesis of myrrhine (*J. Org. Chem.* **2007**, *72*, 2476-2484*)* the following transformation was achieved with amazing selectivity.



E = $CO_2Me$ E = $CO_2Me$

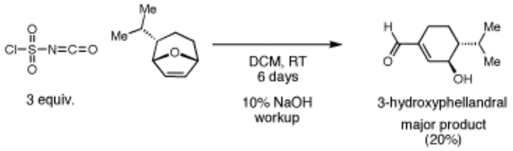
**Part A:** Please provide a 3-dimensional drawing of myrrhine

**Part B:** Please provide a mechanism with 3-dimensional drawings to rationalize the observed selectivity.

### Problem 939

Contributer: **Paul Krawczuk**
Citation: *J. Chem. Soc. Perkin Trans 1* **1993**, 585-587
Keywords: Addition

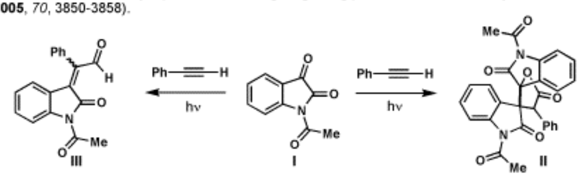
While working on oxa-analouges of the plant growth-promoting agent helminthosporal, Barbosa and coworkers encountered an unexpected rearangement when they treated the bicyclic alkene below with chlorosulfonyl isocyanate (CSI) (*J. Chem. Soc. Perkin Trans.* 1 **1993** 585-587).



## Problem 940

Contributer: **Kyle Eastman**
Citation: *J. Org. Chem.* **2005**, *70*, 3850-3858
Keywords: Addition

Jian-Hua Xu and co-workers recently reported their findings regarding photoreactions of 1-acetylisatin with alkynes (*J. Org. Chem.* **2005**, *70*, 3850-3858).



Propose a mechanism for the conversion of **I** to **II** (*hint* : **III** is also produced).

**Answers**

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Department of Chemistry and Chemical Biology, Harvard University

**Challenging Problems in Chemistry and Chemical Biology**

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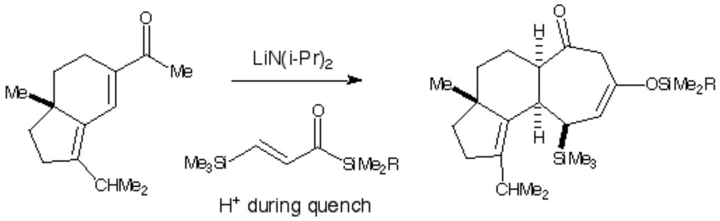
## Problem Answers

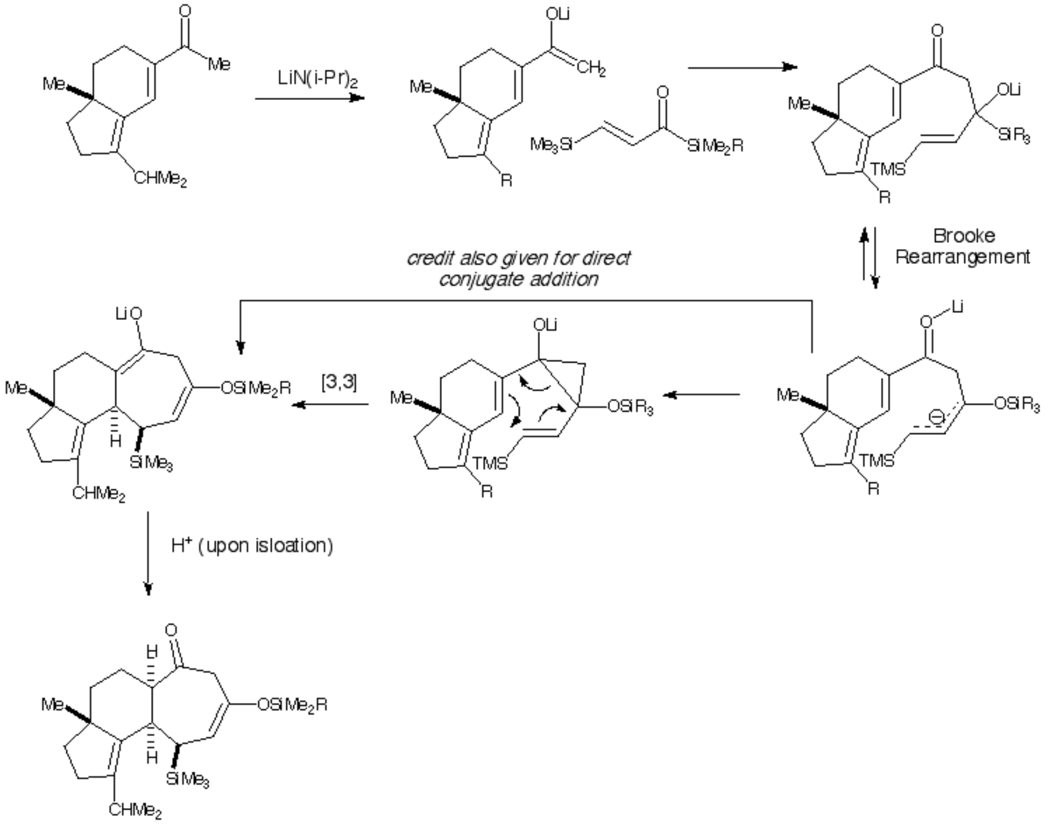
### Problem 10

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2000**, *2*, 1903

Takeda and co-workers have recently reported the mechanistically interesting ring extension reaction illustrated below (*Org. Lett.* **2000**, 2, 1903).



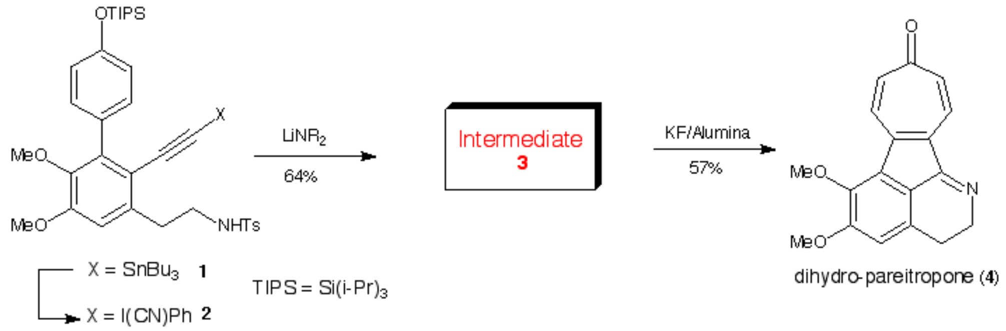
Provide a plausible mechanism for this transformation in the space below.
*Ignore the stereochemical aspect of this transformation.*



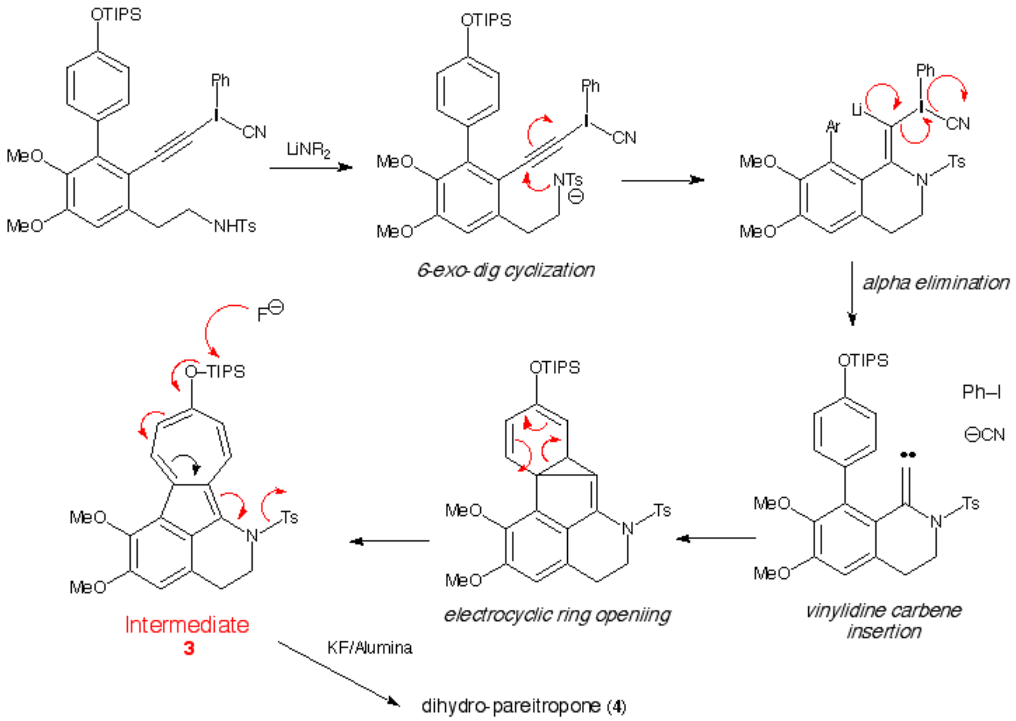
### Problem 12

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2002**, *124*, 11600

An elegant synthesis of pareitropone (**5**) was recently reported by Feldman (*J. Am. Chem. Soc* **2002**, *124*, 11600). The first reaction was staged by the generation of the iodoacetylide **2** which was treated with LiNR$_2$ without purification to form intermediate **3** which was immediately transformed into the dihydro-pareitropone (**4**) in with KF and alumina. The synthesis of **5** was completed by air oxidation of **4**.



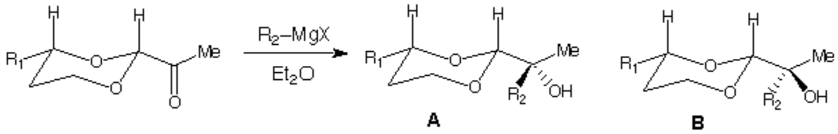
Provide a plausible mechanism for the conversion of **2** to **4** and identify the structure of **intermediate 3**.



## Problem 14

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2001**, *3*, 1865

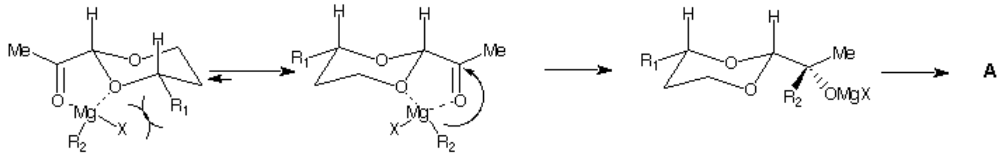
The following carbonyl addition reactions were recently reported by Bailey (*Org. Lett.* **2001**, *3*, 1865-1868). Rationalize the origin of reaction diastereoselelctivity for this addition process.



| | R$_2$–MgX | **A:B** ratio |
|---|---|---|
| R$_1$ = Me | R$_2$ = Ph | 93:7 |
| R$_1$ = CMe$_3$ | R$_2$ = Me | 91:9 |

Provide your answer in the space below:

Chelate Controlled Addition

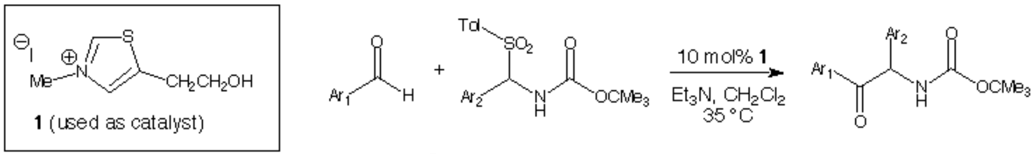


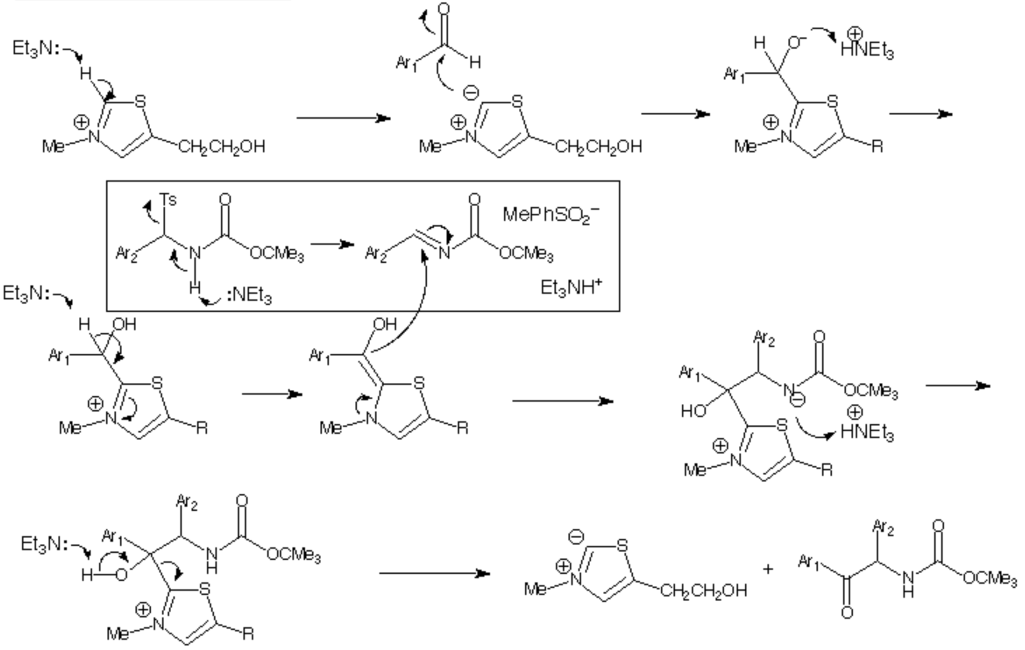
Distal coordination favored on the basis of indicated steric effects

## Problem 16

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2001**, *123*, 9696

The reaction illustrated below was recently reported by Murry and co-workers from the Merck Process Group (*JACS* **2001**, *123*, 9696-9697). Provide a mechanism for this transformation in the space below.

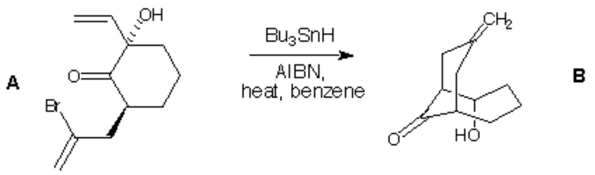




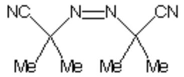
## Problem 18

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2001**, *3*, 1181-1183

The following transformation was recently reported by Rodriguez (*Org. Lett.* **2001**, *3*, 1181-1183).

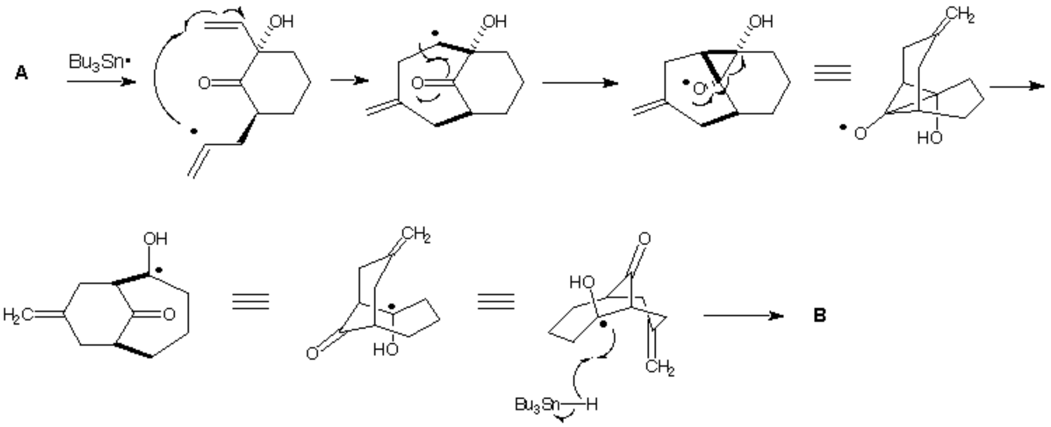


**Part A** What is the structure and function of AIBN in this reaction?



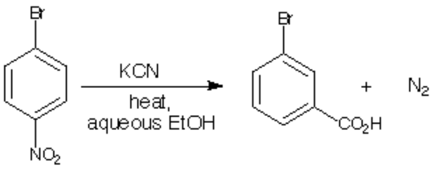
AIBN functions as a radical initiator

**Part B** Provide a mechanism for the illustrated rearrangement(s) of **A** to **B.** Where stereochemical issues are present, provide clear three dimensional drawings to support your answer.

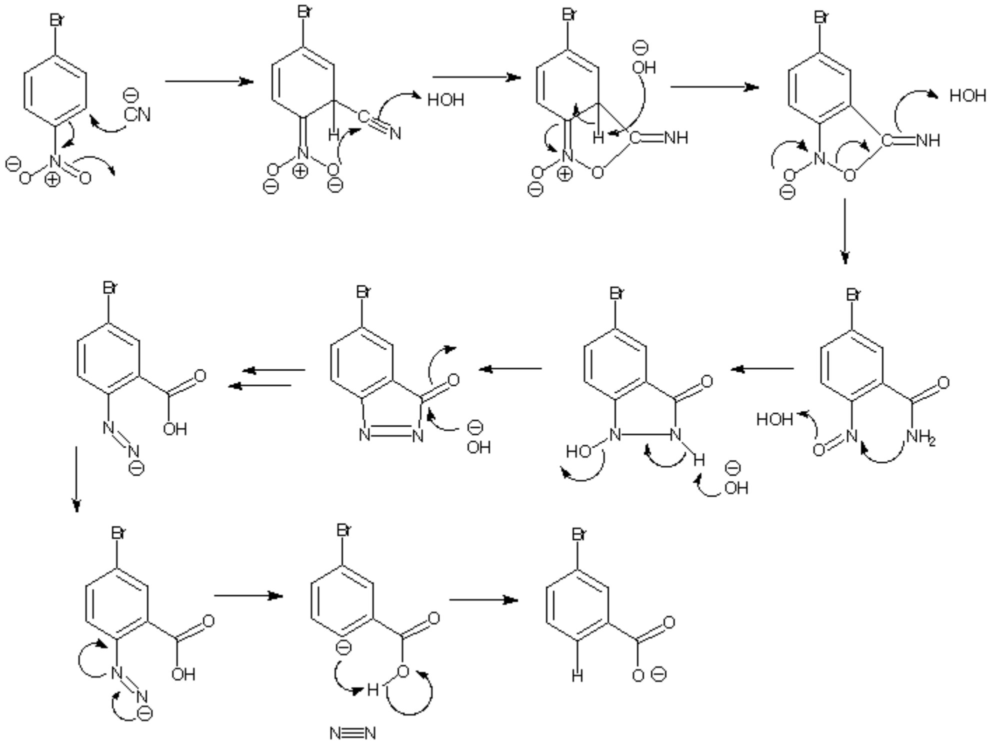


**Problem 21** Contributer: **David A. Evans**
Citation:

The **Von Richter** reaction is illustrated in the accompanying equation. Please provide a plausible mechanism for this transformation taking into account the following observations. (a) If $^{15}$N-labeled KCN is used, the $N_2$ formed is half labeled; (b) 3-bromo-benzonitrile does not form 3-bromo-benzoic acid under the reaction conditions.



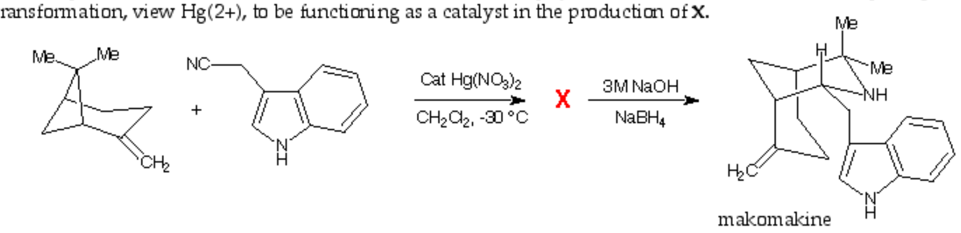
Provide your answer in the space below:



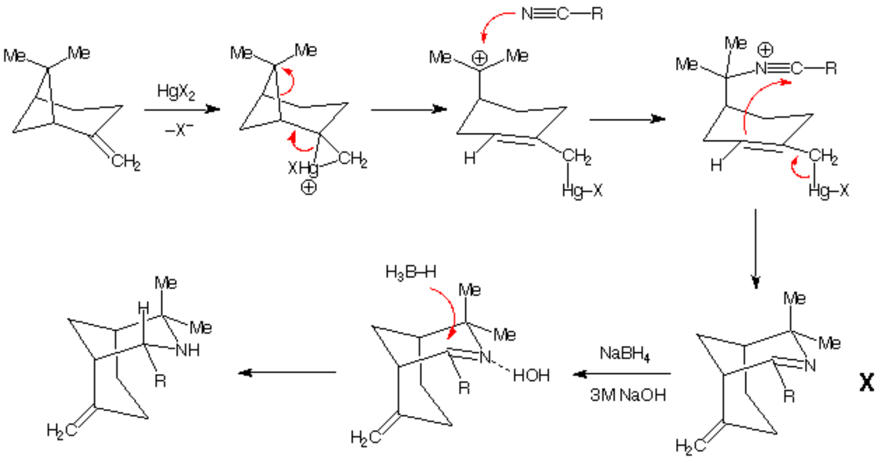
## Problem 22

Contributer: **David A. Evans**
Citation: *Chem. Commun.* **1983**, 384

An interesting example of the **Ritter Reaction** was reported some time ago by R. V. Stevens (*Chem. Comm.* 384 **1983**). The relevant process illustrated below afforded an efficient two-step synthesis of makomakine. In contemplating this transformation, view Hg(2+), to be functioning as a catalyst in the production of **X**.



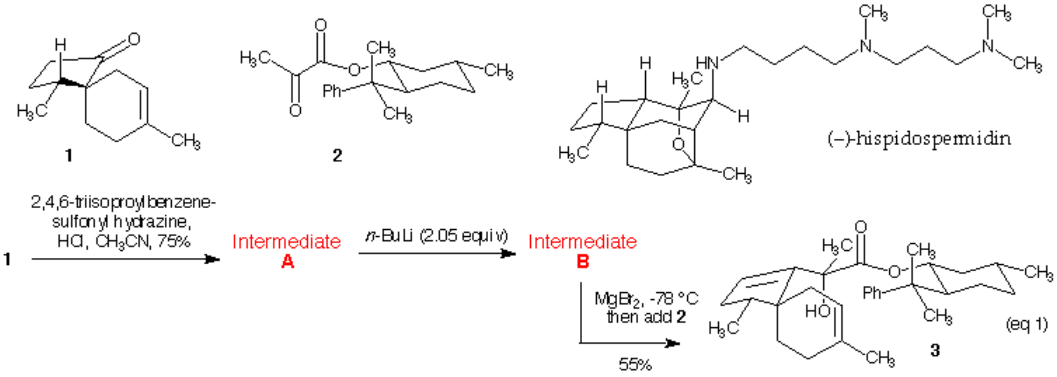
In the space below, provide a mechanism for the illustrated two-step transformation and identify the structure **X**.



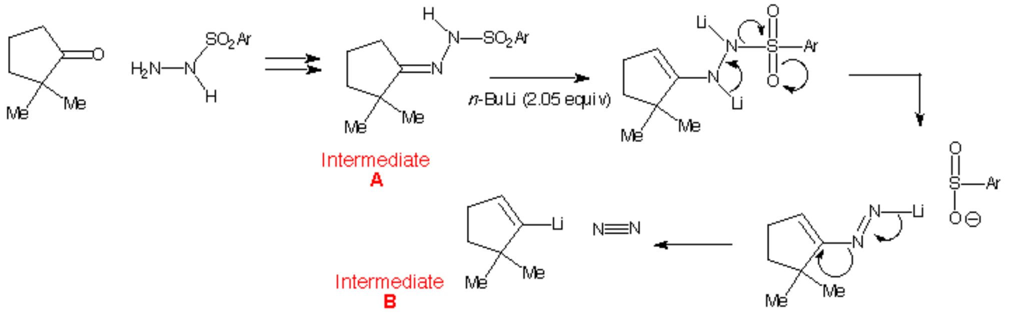
## Problem 24

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2000**, *122*, 9556

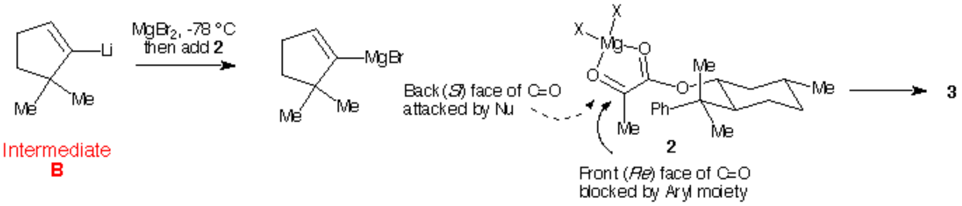
Sorensen and coworkers recently reported the synthesis of (–)-hispidospermidin (Sorensen *J. Am. Chem. Soc.* **2000**, *122*, 9556). The **Shapiro Reaction**, along with methodology developed by Whitesell, was use in the construction of intermediate **3** from the indicated building blocks **1** and **2** (eq 1).



**Part A.** Provide a mechanism for the **Shapiro Reaction** of **1** to intermediate **B** in the space below. Feel free to use a simplified analog of **1** such as 2,2-dimethylcyclopentanone to answer this question.



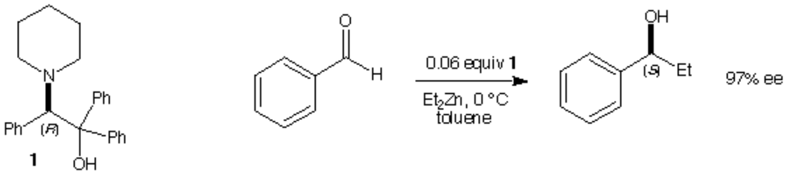
**Part B.** Provide a mechanism for the **transformation** of intermediate **B** to the illustrated product **3.** Use 3-dimensional representations to illustrate the stereochemical aspects of this individual step.


MgBr2, -78 °C then add 2
Intermediate B
Back (Si) face of C=O attacked by Nu
Front (Re) face of C=O blocked by Aryl moiety
2
3

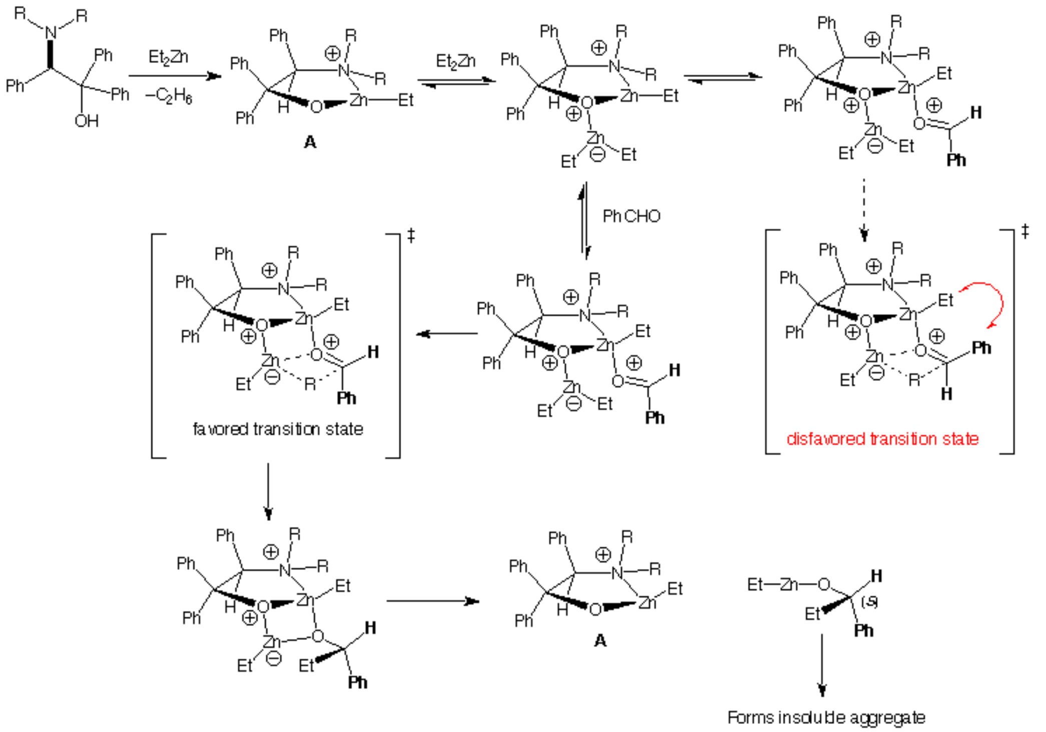
## Problem 27

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2000**, *65*, 7303

Chiral amino alcohol **1** efficiently mediates the addition of diethylzinc to aromatic aldehydes. While a number of other amino alcohols are also effective in controlling the absolute course of the addition process, this amino alcohol has been the focus of a recent computational investigation that addresses the preferred transition state geometry for this addition process (Pericas, et al. *J. Org. Chem.* **2000**, *65*, 7303 and references cited therein). It should be noted that, while **1** is not the actual catalyst, it is modified under the reaction conditions to the competent catalytic agent.

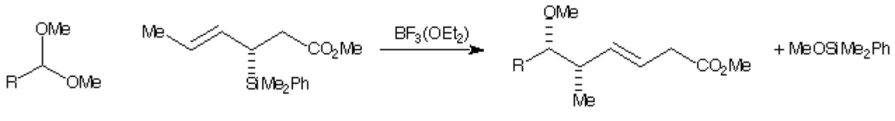


Provide a detailed mechanism for the overall transformation in the space below. Use three-dimensional representations to illustrate the absolute stereochemical aspects of the indicated transformation.



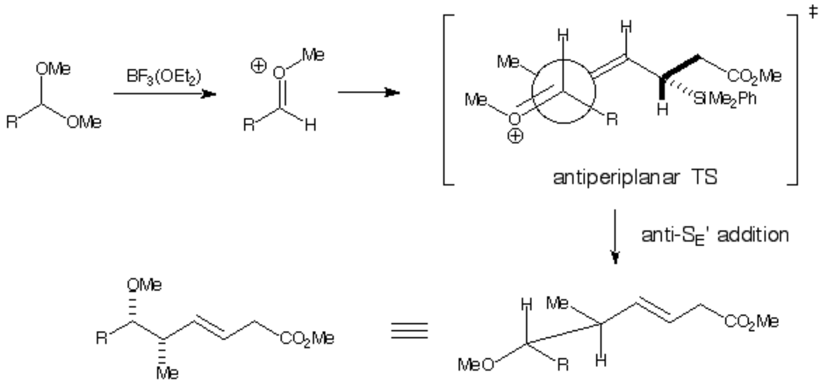
**Problem 29** Contributer: **David A. Evans**
Citation: *Chem. Rev.* **1995**, *95*, 1293-1316

In his seminar in CCB on April 17, 2000, Professor Panek described a number of diastereoselective transformations based on chiral allylsilanes. One such transformation is provided below.



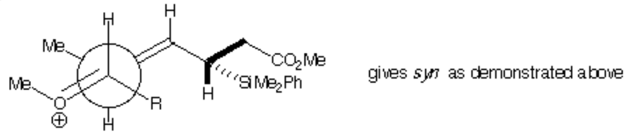
*syn/anti diastereoselection 2–40:1*

**Part A.** Provide a detailed mechanism for the illustrated transformation in the space below. Use three-dimensional representations, where relevant, illustrate the stereochemical aspects of the individual steps.

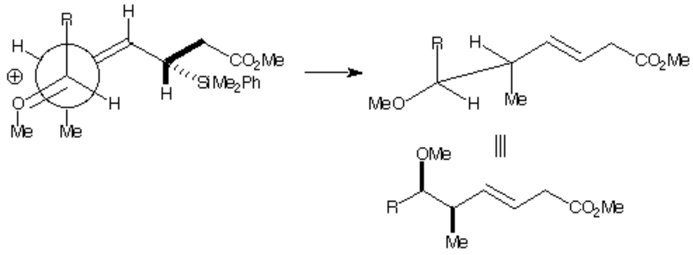


**Part B.** In principle, both *syn* and *anti* product diastereomers are possible. In the space below, rationalize the preference for *syn* reaction diastereoselection from both allylsilane geometries. Use antiperiplanar transition states.

*E* crotyl silane:



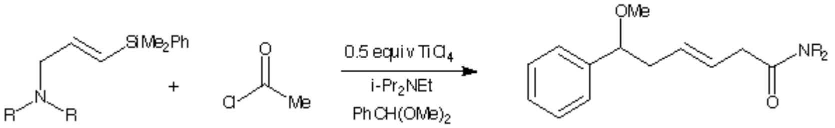
*Z* crotyl silane:



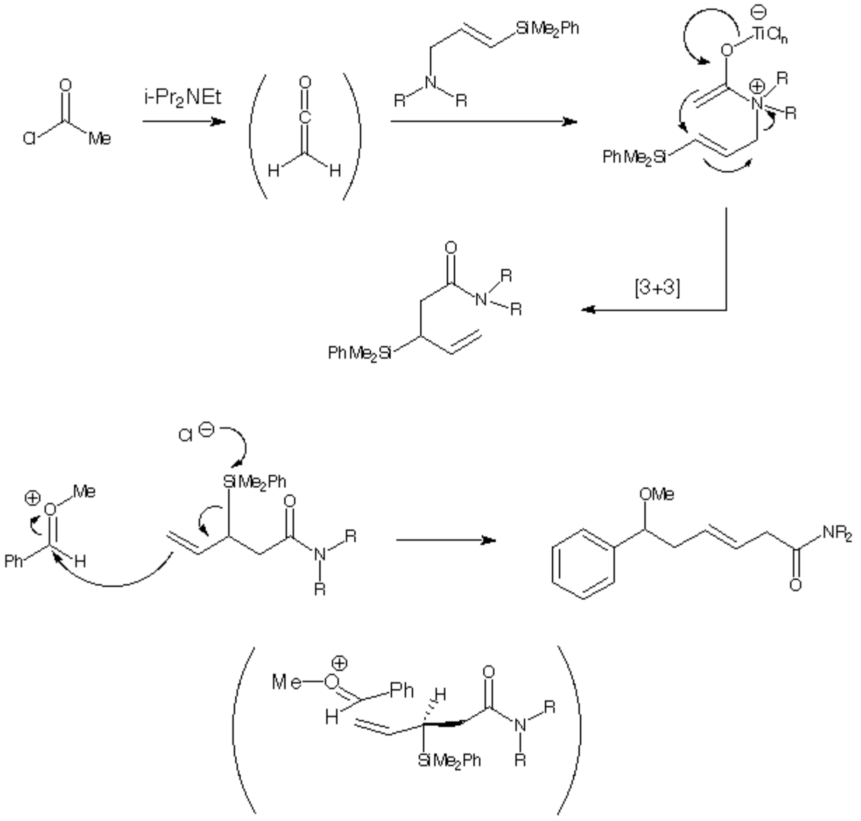
**Problem 31**

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1999**, *121*, 9726

In the Panek lecture he described the transformation illustrated below. This transformation is an extrapolation of the recent publication of MacMillan and co-workers (*JACS*, **1999**, *121*, 9726).



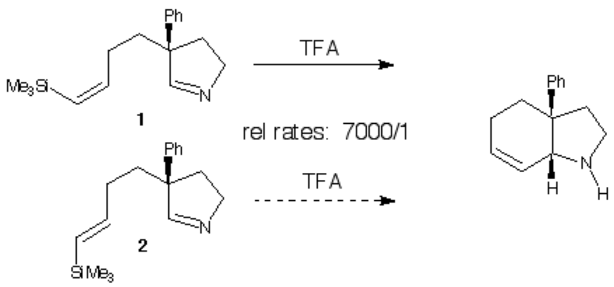
Provide a detailed mechanism for the illustrated transformation. Use three-dimensional representations, where relevant, to illustrate the stereochemical aspects of the individual steps.



Alignment of crotylsilane necessary for *trans* olefin geometry

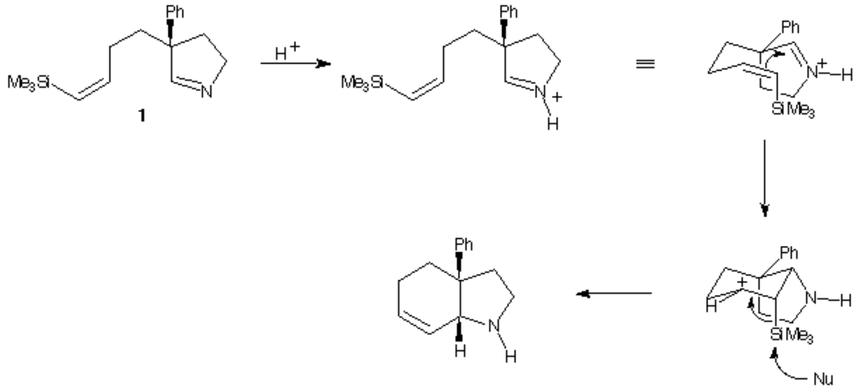
**Problem 32** Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1984**, *25*, 5739

Overman carried out the cyclizations of the illustrated (E) and (Z) vinylsilanes **1** and **2**, both of which afforded the indicated product (Overman et al. *TL* **1984**, *25*, 5739). He observed that **1** cyclizes 7000-times faster than **2**.

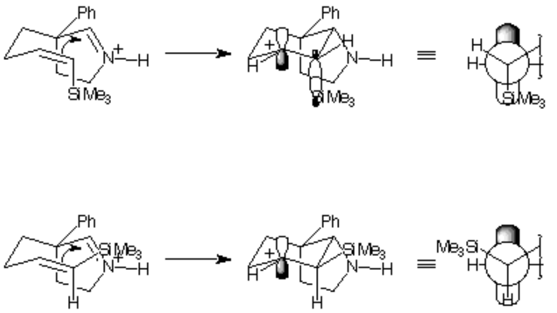


Overman et al. *TL* **1984**, *25*, 5739.

**Part A.** Provide a detailed mechanism for the transformation of **1** and **2** to the illustrated product. Use three-dimensional representations, where relevant, to illustrate your answer.



**Part B.** In addition, rationalize the illustrated rate difference for the individual cyclizations.



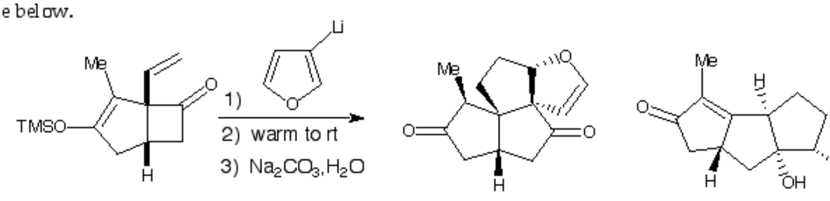
*The rate difference between the stereoisomers is most likely due to the presence of $\sigma_{Si\text{-}C} \rightarrow \pi_p$ stabilization (hyperconjugation) of the developing β-silyl cation in the transition state which is only possible from the Z-alkene. Efficient orbital overlap (Newman projection) only occurs with axial disposition of the TMS group.*

**Problem 37** Contributer: **David A. Evans**
Citation: *Synthesis* **1996**, 285

Consult the cited reference for an answer to this question

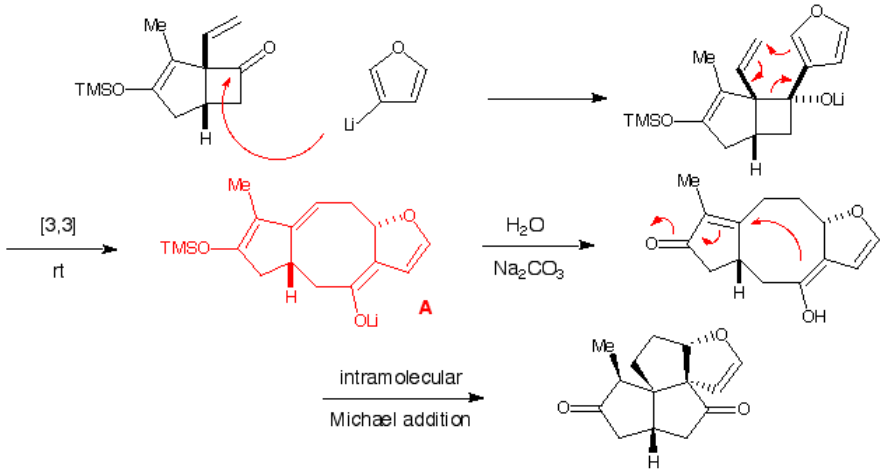
**Problem 43** Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1996**, *61*, 7976

Moore (*J. Org. Chem.* **1996**, *61*, 7976) recently reported the elegant 3-step transformation that is illustrated by the specific example below.

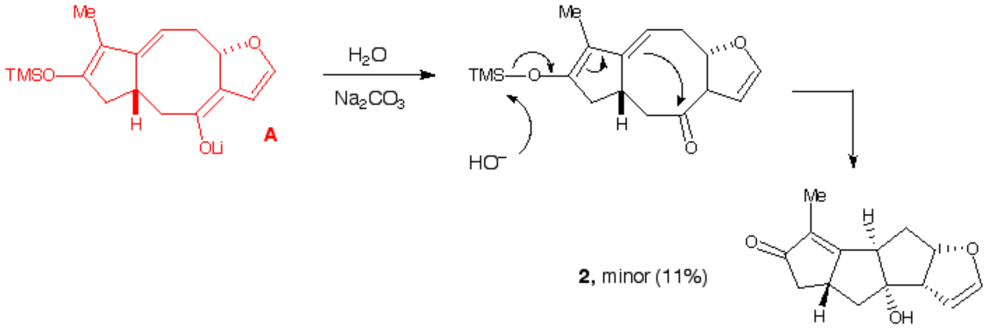


**1,** major (57%) **2,** minor (11%)

**Part A.** Draw out a plausible mechanism for the transformation to the major product isomer **1.**



**Part B.** Draw out a plausible mechanism for the transformation to the minor product isomer **2.**

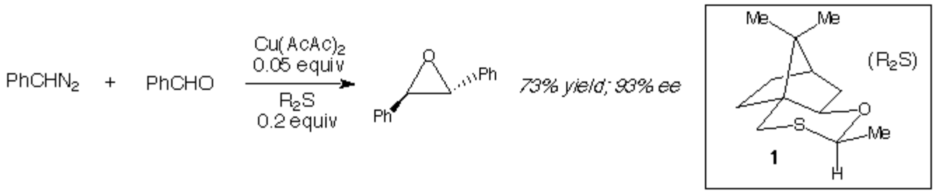


**2,** minor (11%)

**Problem 44**

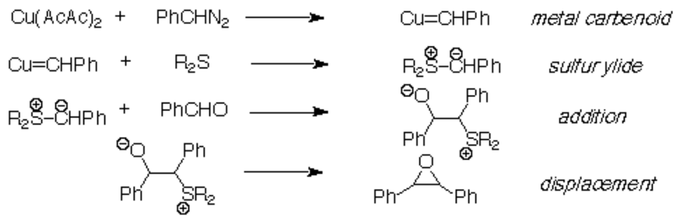
Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1996**, *118*, 7004

Aggarwal (*J. Am. Chem. Soc.* **1996**, *118*, 7004) recently reported the enantioselective aldehyde epoxidation illustrated below. One of the important issues to be addressed in this question is how **1**, used in sub-stoichiometric quantities, is capable of controling the absolute stereochemical outcome of the process. *The absolute configurations of both* **1** *and stilbene oxide are as illustrated.* Provide answers to the two questions pertaining to this transformation posed below and on the following page.

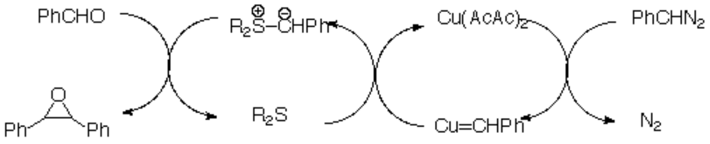


**Part A.** Draw out each of the steps in this transformation. Since you are not asked to address the stereochemical aspects of the reaction here, **1** may be simplified as $R_2S$. At the bottom of the page draw out the catalytic cycle.

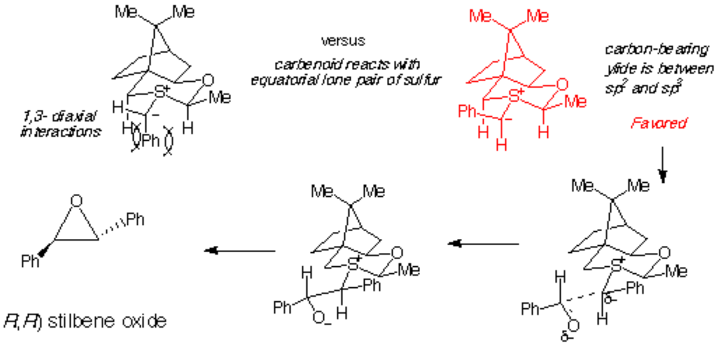
**Steps:**



**Catalytic Cycle:**

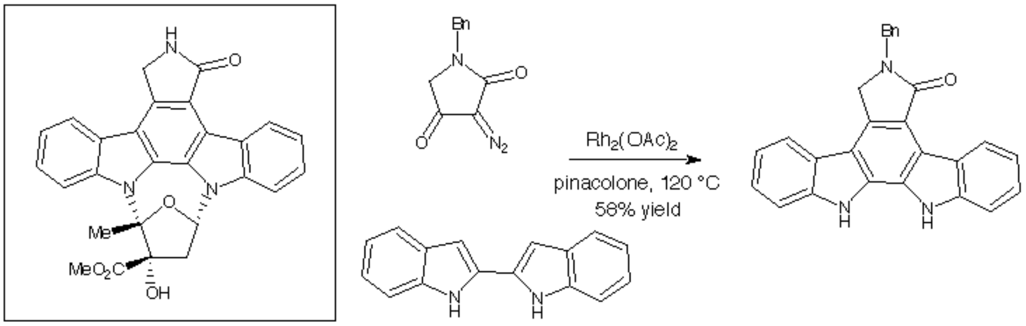


**Part B .** Clearly explain how **1** imparts chirality to the epoxidation process. Your answer should clearly explain the absolute stereochemical outcome of the process.

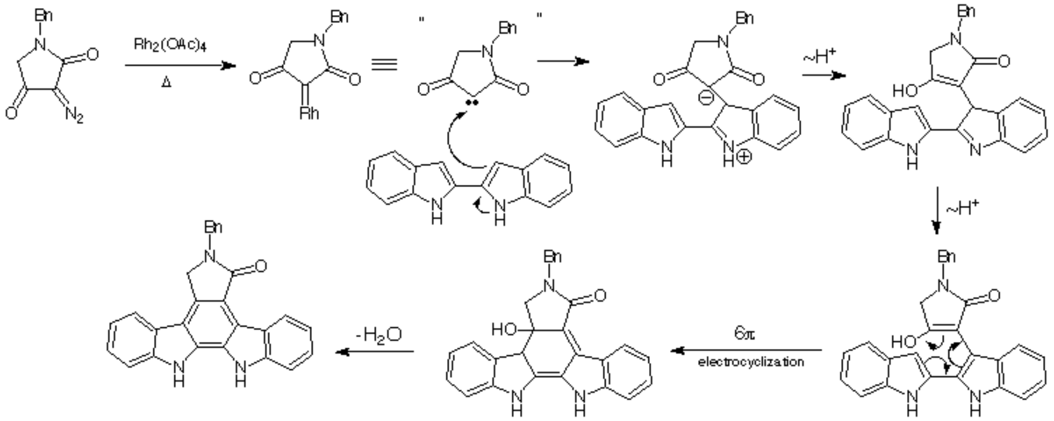

Me
Me
O
S+
Me
H
H
H
Ph
1,3- diaxial interactions
versus
carbenoid reacts with equatorial lone pair of sulfur
Me
Me
O
S+
Me
Ph
H
H
H
carbon-bearing ylide is between sp2 and sp3
Favored
O
Ph
Ph
(R,R) stilbene oxide
Me
Me
H
S+
O
Me
Ph
Ph
O
H
Me
Me
O
S+
Me
H
Ph
Ph
δ-
O
δ-
H

**Problem 47** Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1995**, *117*, 10413

Wood recently reported a very clever approach to the synthesis of the indolocarbazole family of natural products (*JACS* **1995**, *117*, 10413). His approach to the indolocarbazole core is the one-pot transformation outlined below.



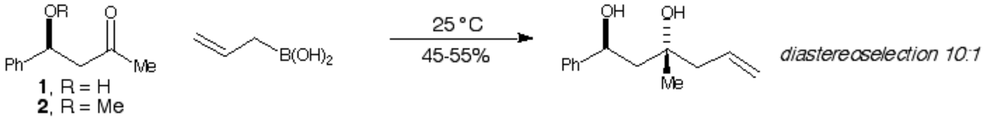
Provide a plausible mechanism for this multi-step transformation in the space below.



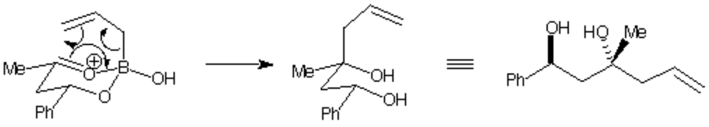
## Problem 48

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1996**, *37*, 2181

The following transformation was recently reported by Kabalka (*Tetrahedron Lett.* **1996**, *37*, 2181). Treatment of **1** with allylboronic acid afforded the indicated adduct in high yield with 10:1 diastereoselection. On the other hand, the analogous reaction of **2** was nonstereoselective. Propose a mechanism for this transformation that accounts for the stereochemical outcome of the addition process.



**1**, R = H
**2**, R = Me

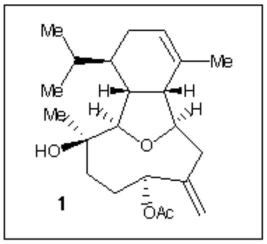


cyclic transition state with all substituents equatorialtransesterification not possible with OMe ether

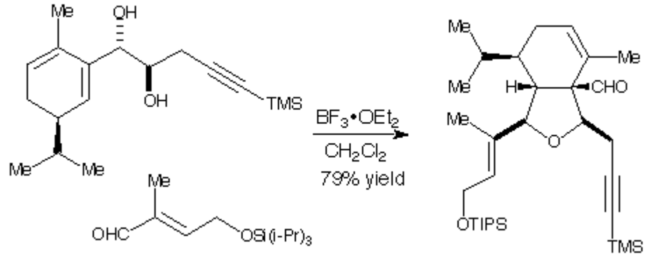
## Problem 49

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1995**, *117*, 10391

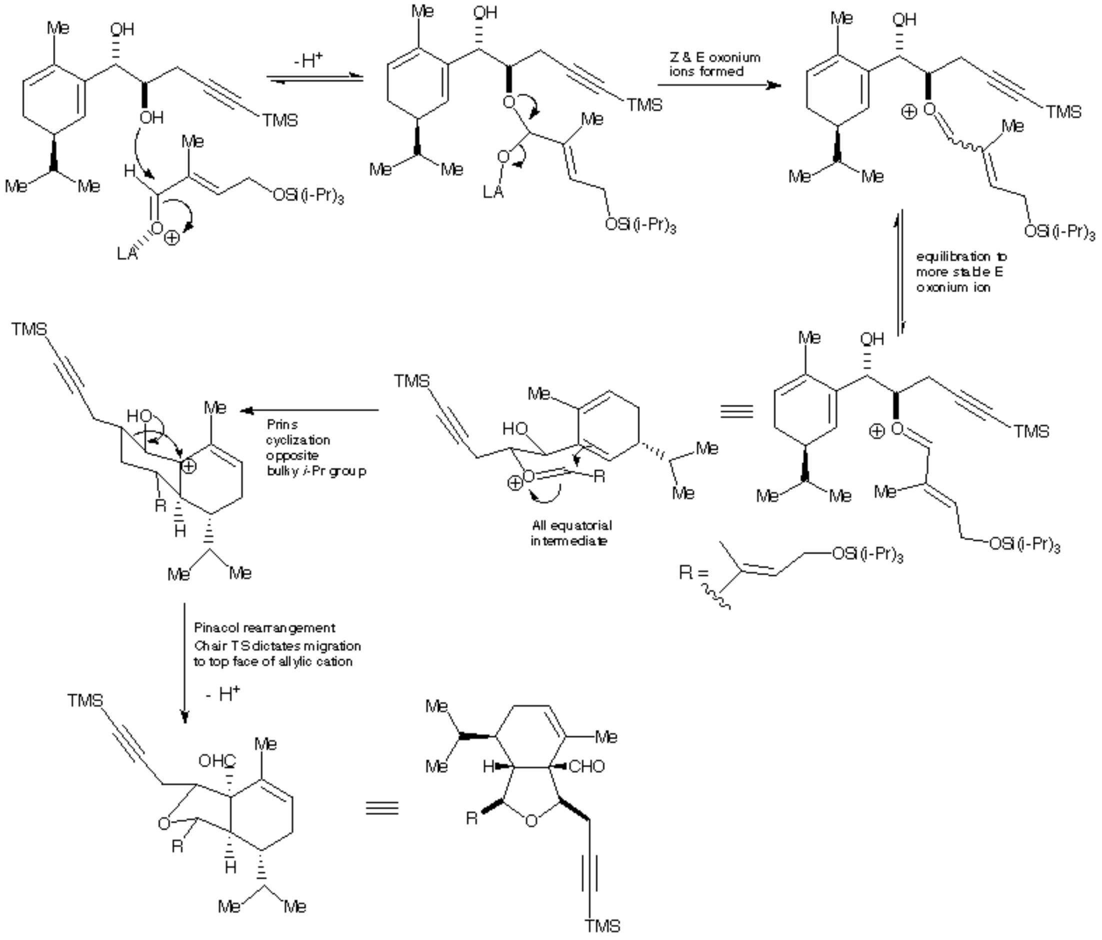
Overman and MacMillan (*JACS* **1995**, *117*, 10391) recently reported the synthesis of the diterpene, 7-deacetoxyalcyonin (**1**) illustrated below. The keynote reaction in this synthesis is the Lewis acid catalyzed transformation illustrated below, a process that has previously been investigated in the Overman Group (*JACS* **1991**, *113*, 3534).



**1**



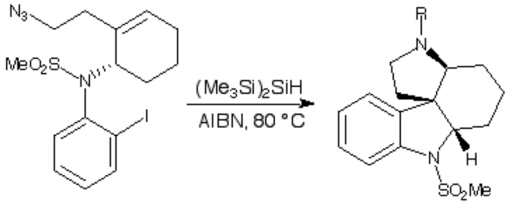
Propose a detailed mechanism for this transformation. Be sure to clearly identify the stereochemical control elements that are operating in the creation of the new stereogenic centers.


- H$^+$
Z & E oxonium ions formed
equilibration to more stable E oxonium ion
Prins cyclization opposite bulky *i*-Pr group
All equatorial intermediate
R =
Pinacol rearrangement
Chair TS dictates migration to top face of allylic cation
- H$^+$

**Problem 50**

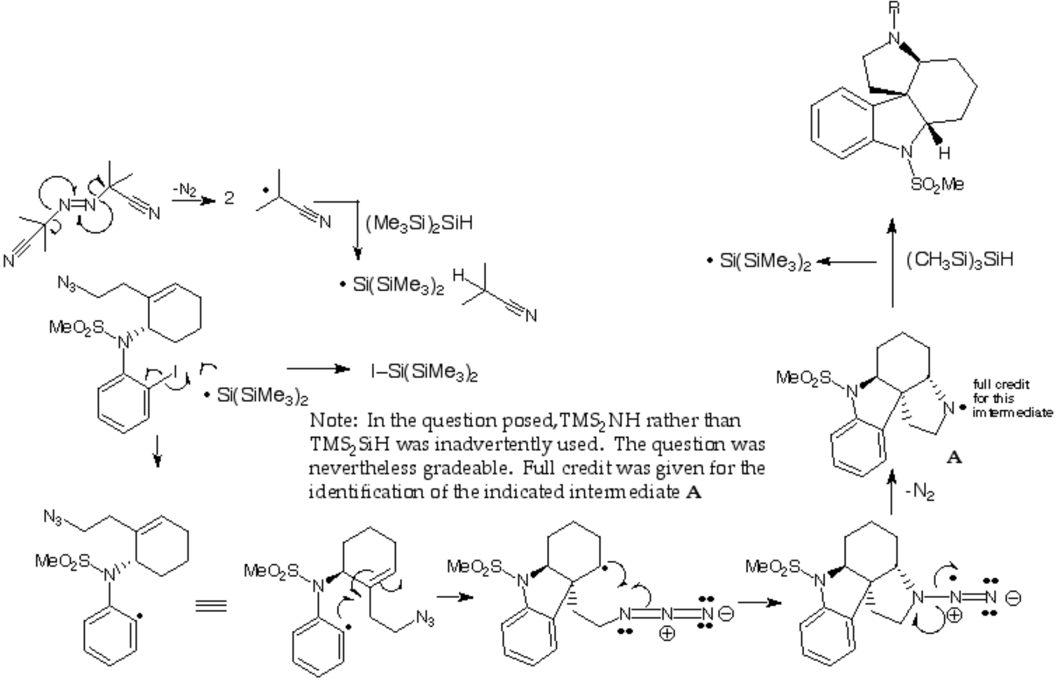
Contributer: **David A. Evans**
Citation: *Chem. Commun.* **1995**, 1409

Murphy (*Chem. Comm.* **1995**, 1409) recently reported a very efficient approach to the synthesis of the aspidosperma alkaloid skeleton (eq 1).



(1)

Provide a plausible mechanism for this transformation in the space provided below.

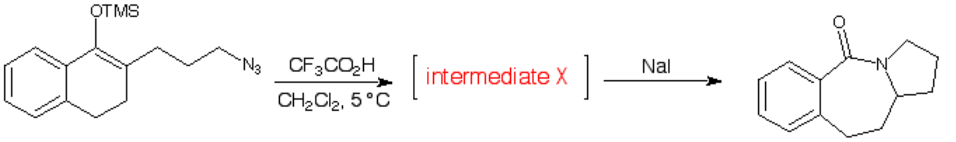


Note: In the question posed, TMS$_2$NH rather than TMS$_2$SiH was inadvertently used. The question was nevertheless gradeable. Full credit was given for the identification of the indicated intermediate **A**

## Problem 51

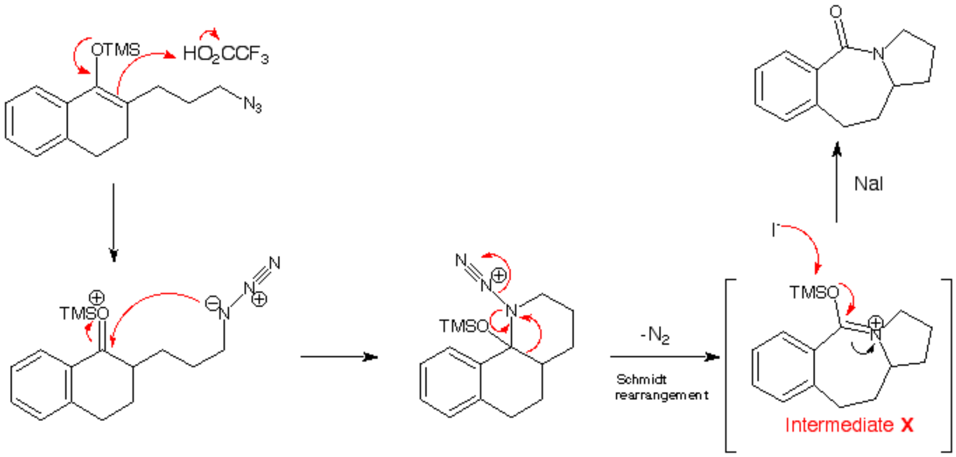
Contributer: **David A. Evans**
Citation: *Tetrahedron* **1996**, *52*, 3403

Aube (*Tetrahedron* **1996**, 52, 3403) recently reported an efficient approach to the synthesis of polycyclic lactams. A typical transformation is provided below (eq 2).



(2)

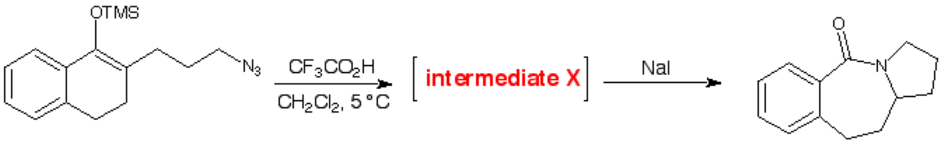
Provide a plausible mechanism for this transformation in the space below.



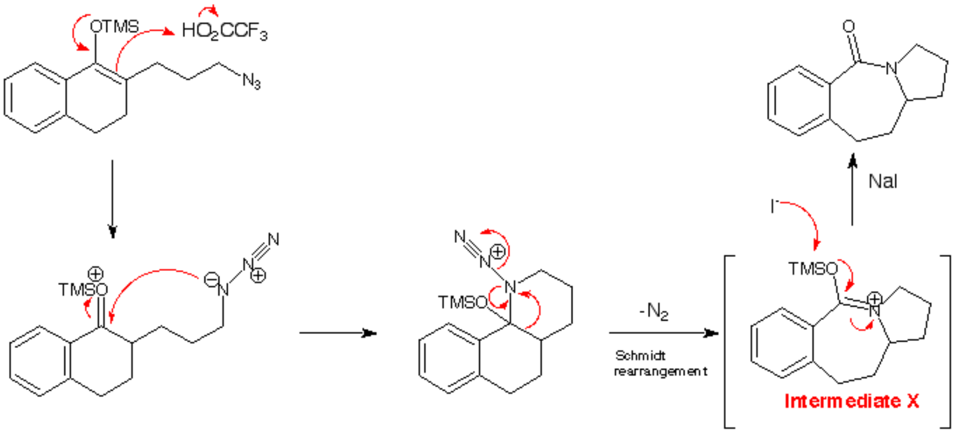
## Problem 54

Contributer: **David A. Evans**
Citation: *Tetrahedron* **1996**, *52*, 3403

Aube (*Tetrahedron* **1996**, 52, 3403) recently reported an efficient approach to the synthesis of polycyclic lactams. A typical transformation is provided below.



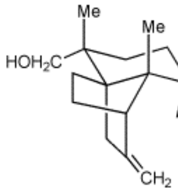
Provide a plausible mechanism for this transformation in the space below.



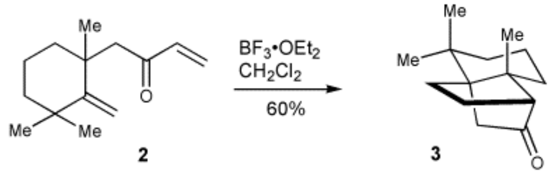
## Problem 56

Contributer: **Grace Wang**
Citation: *Chem. Commun.* **1994**, 2259

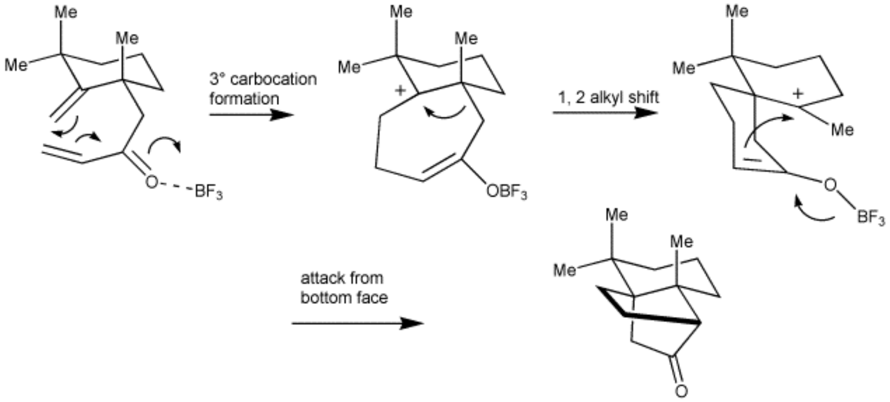
The recently isolated irregular sesquiterpene myltaylenol (**1**) stimulated Srikrishna and co-workers (*Chem Commun*. **1994**, 2259) to study the biogenetically modeled acid-promoted rearrangement of **2** which leads to the desired terpenoid skeleton in good yield. In the space below provide a detailed mechanism for the transformation of **2** to **3**.



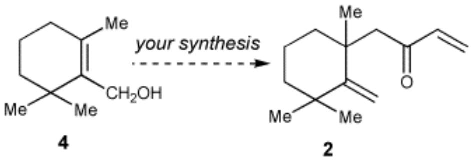
*myltaylenol*
**1**

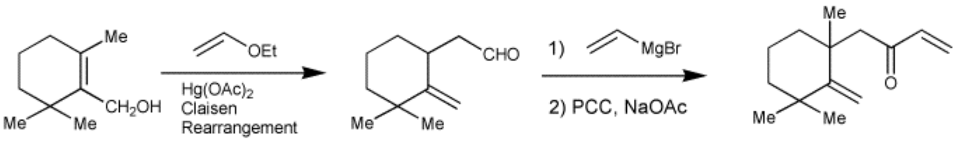


**Part A.** Provide a mechanism for the transformation of **2** to **3**.



**Part B.** Provide an expedient synthesis of **2** from the allylic alcohol **4**.



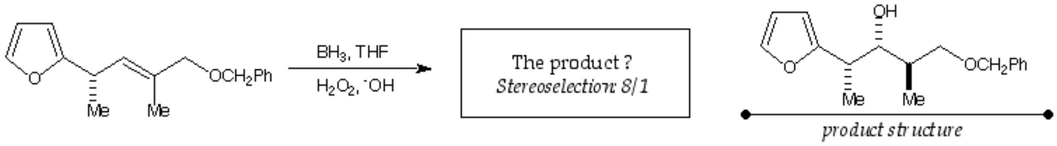


**Problem 60** Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1987**, *28*, 1267

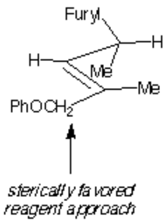
Consult the cited reference for an answer to this question

**Problem 61** Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1979**, *101*, 259

The following stereoselective hydroboration has been reported by Kishi in his synthesis of monensin (*JACS* **1979**, *101*, 259). Provide the stereostructure of the major product and rationalize the stereochemical outcome as indicated in the directions.



**The rationalization ?**



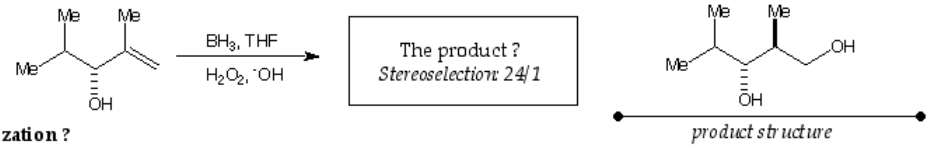
The two olefin diastereofaces experience a bias imposed by the allylic furyl and methyl substituents. The conformation of the substrate (and transition states evolving from these conformations) is dominated by A(1,3) allylic strain effects. Presuming that the furyl substiltuent is sterically more demanding that the methyl substituent, the indicated direction of the hydroboration rationalizes the observed major product.

**Reading List:**
- The Kishi monensin synthesis (*JACS* **1979**, *101*, 259).
- The A(1,3) Strain Review article by Hoffmann *Chem. Rev.* **1989**, *89*, 1841-1860.
- The theoretical analysis by Houk *Tetrahedron* **1984**, *40*, 2257-2274

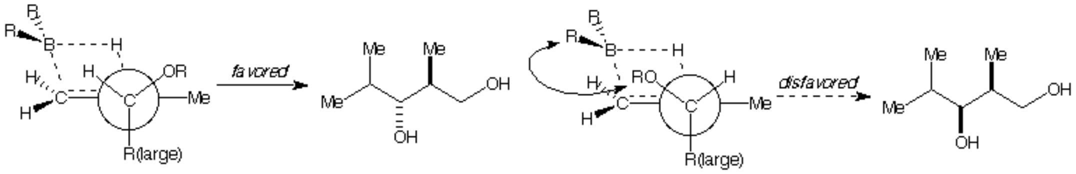
## Problem 62

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1983**, *105*, 2487

The following stereoselective hydroboration has been reported by Still ( *JACS* **1983**, *105*, 2487).
Provide the stereostructure of the major product and rationalize the stereochemical outcome as indicated in the directions.



**The rationalization ?**



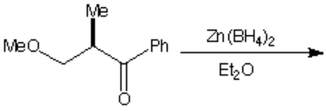
The model proposed to explain this reaction is provided above. The destabilizing interaction in the disfavored transition state is indicated above. This is essentially the model proposed by Still and verified by Houk.

**Reading List:**
- The Still paper, *JACS* **1983**, *105*, 2487
- The theoretical analysis by Houk *Tetrahedron* **1984**, *40*, 2257-2274

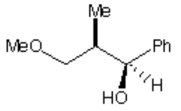
## Problem 63

Contributer: **David A. Evans**
Citation: *Chem. Pharm. Bull. Japan* **1984**, *32*, 1411

The following stereoselective reduction has been reported by Oishi (*Chem. Pharm. Bull.* **1984**, *32*, 1411).
Provide the stereostructure of the major product and rationalize the stereochemical outcome as indicated in the directions.



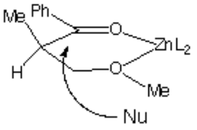
The product ?
*Stereoselection: 32/1*



*product structure*

**The rationalization ?**

This is a typical example of a chelate-organized reduction: In this instance, the substrate is organized through bidentate chelation with the metal ion and the nucleophile attacks the carbonyl diastereoface opposite to the methyl substituent.



**Reading List:**

For a recent relevant study on chelate-organized C=O addition see:
Eliel, *JACS*, **1992**, *114*, 1778-1784, and cited references

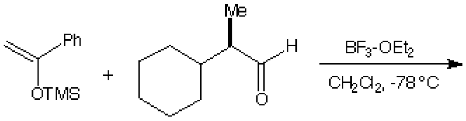
For a general review or chelate-organized processes see:
Reetz, *Angew. Chem. Int. Edit.*, **198423**, 556-569

See also the complementary review by Oishi:
*Accts Chem. Research*, **1984**, *17*, 556-569

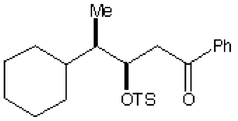
## Problem 64

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1983**, *105*, 1667

The following stereoselective aldol addition reaction has been reported by Heathcock (*J. Am. Chem. Soc.* **1983**, *105*, 1667).
Provide the stereostructure of the major product and rationalize the stereochemical outcome as indicated in the directions.

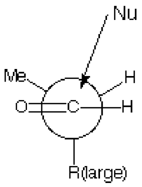


The product ?
*Stereoselection: 16/1*



*product structure*

**The rationalization ?**



The Felkin-Anh model is now widely employed to rationalize the stereochemical course of carbonyl addition:

**Reading List:**

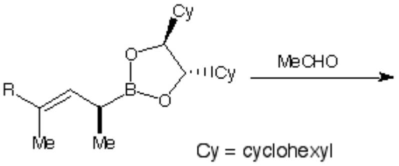
For the discussion of the Felkin-Anh model see:
Anh & Eisenstein, *Nouv. J. Chim.* **1977**, *1*, 61-70

For several theoretical studies supporting this model see:
Houk, *JACS*, **1987**, *109*, 908-910.
Padden-Row, *Chem. Commun.* **1990**, 456-8.

## Problem 66

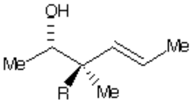
Contributer: **David A. Evans**
Citation: *Liebig's Ann. Chem.* **1991**, 1203

The following stereoselective transformation has been reported by Hoffmann (*Liebig's Ann. Chem.* **1991**, 1203).
Provide the stereostructure of the major product and rationalize the stereochemical outcome as indicated in the directions.



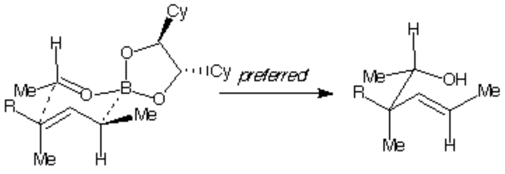
Cy = cyclohexyl

The product ?
*Stereoselection: >20:1*



*product structure*

**The rationalization ?**

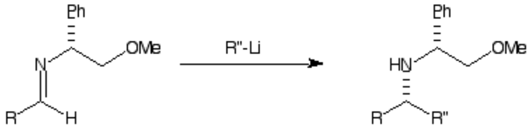


A(1,3) effects define the low-energy conformation of the allylboronate-RCHO transition state. In this instance, the oxygen-bearing stereogenic centers are subordinate to the organization provided by the boron-bearing stereogenic center. See the Hoffmann review, pp 1849-51.

## Problem 69

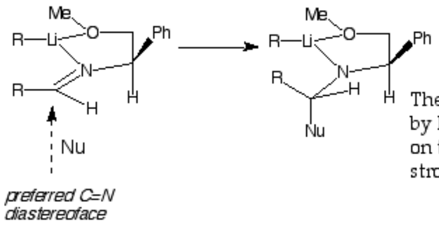
Contributer: **David A. Evans**
Citation: *Chem. Lett.* **1991**, 1555

The following stereoselective transformation has been reported by Fujisawa (*Chem.Lett.* **1991**, 1555). Given the stereochemistry of the product, rationalize the stereochemical outcome of the indicated reaction.



stereoselection >97:3

**The rationalization ?**



The stereochemical outcome of this reaction has been rationalized by Fujisawa through the chelate-organized imine complex shown on the left. In this study diastereoface selectivity was noted to be strongly dependant on the nature of the organometallic reagent.

## Problem 71

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1991**, 3608

Consult the cited reference for an answer to this question

## Problem 74

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1988**, *110*, 5192

Consult the cited reference for an answer to this question

## Problem 77

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1988**, *110*, 3948

Consult the cited reference for an answer to this question

## Problem 78

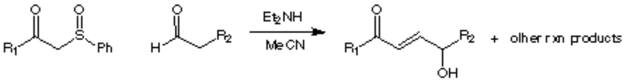
Contributer: **David A. Evans**
Citation: *Chem. Commun.* **2003**, 276

Consult the cited reference for an answer to this question

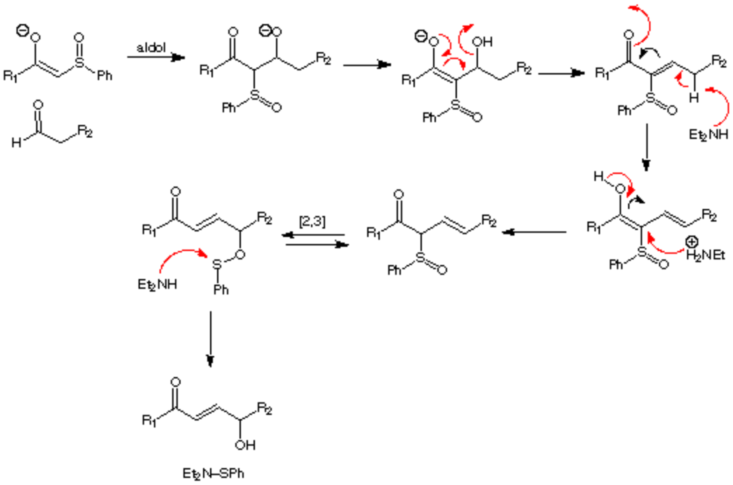
## Problem 83

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2001**, *66*, 1228

The illustrated Knovenagel-type condensation recently reported by Nokami et al. (*J. Org. Chem.* 2001, *66*, 1228) should prove to be a generally useful transformation.



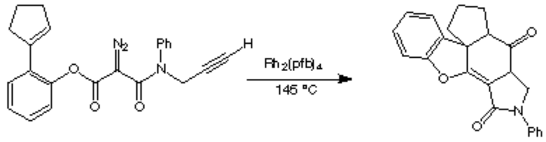
In the space below, provide a mechanism for the indicated transformation.



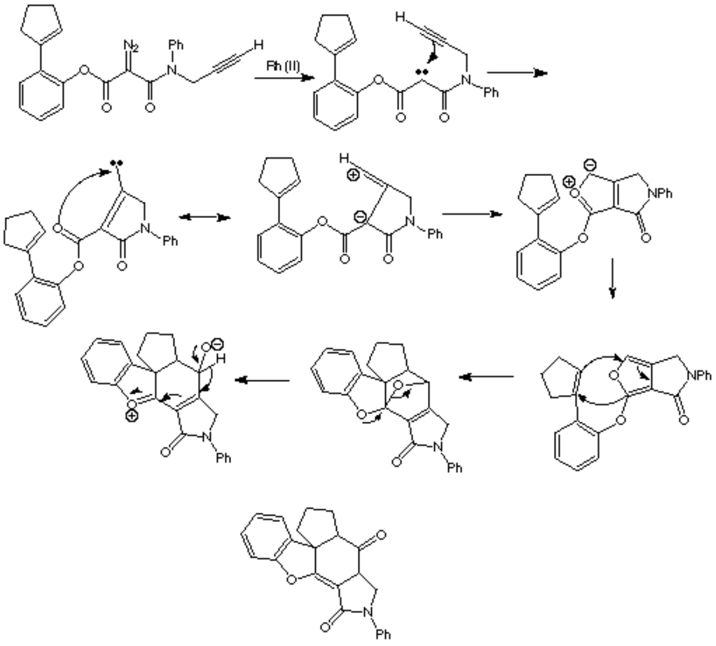
### Problem 89

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2001**, *ASAP*,

Padwa and co-workers recently disclosed the illustrated multistep polycyclisation as a possible route to the strychnine core (*Org. Lett.* 2001, ASAP)



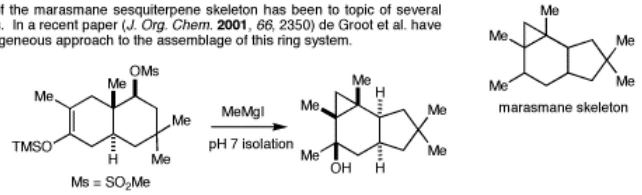
In the space below, provide a mechanism for the indicated transformation. *Hint: The management suggests that a carefull bidirectional analysis might help you to arrive at a solution of this question.*



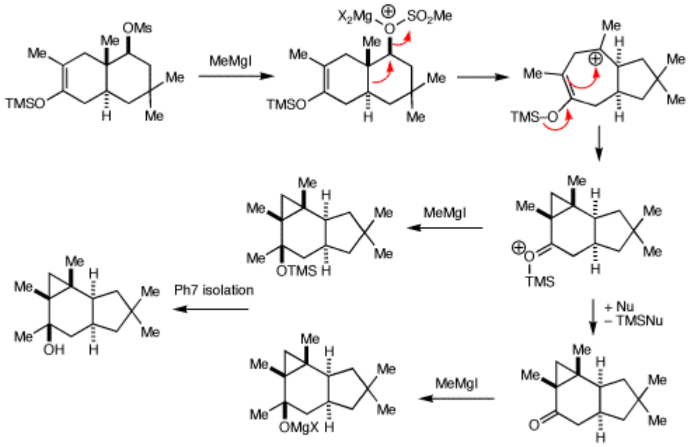
### Problem 90

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2001**, *66*, 2350

The synthesis of the marasmane sesquiterpene skeleton has been to topic of several research groups. In a recent paper (*J. Org. Chem.* **2001**, *66*, 2350) de Groot et al. have developed an ingeneous approach to the assemblage of this ring system.



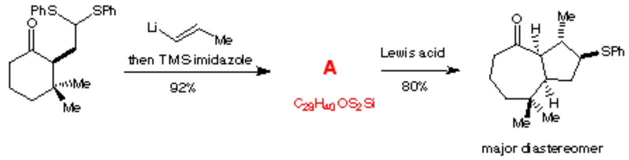
In the space below, provide a mechanism for the indicated transformation.



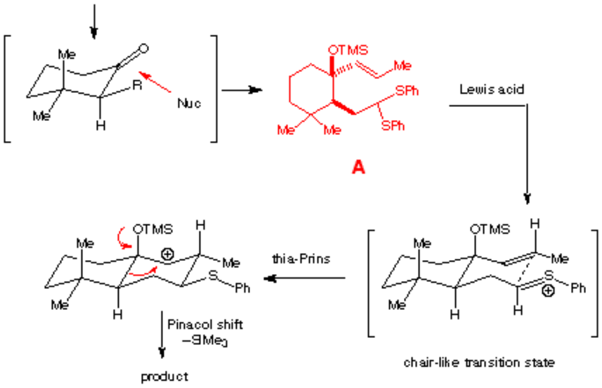
## Problem 92

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2001**, *123*, 4851

In Overman's synthesis of shahamin K (*J. Am. Chem. Soc.* 2001, *123*, 4851), the key transformtion involves the interesting reaction sequence shown below.



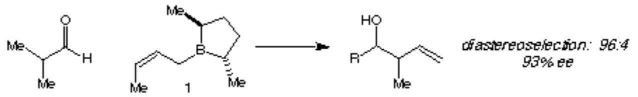
Please provide a mechanism for this two-step process and identify intermediate A.



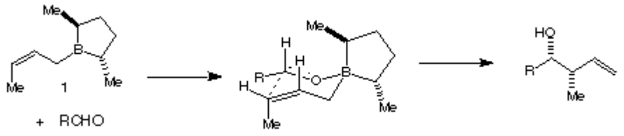
## Problem 93

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1987**, *52*, 4831

S. Masamune has reported the illustrated allylboration (*J. Org. Chem.* 1987, *52*, 4831).



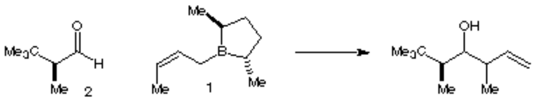
Predict the stereochemical outcome of the reaction and draw the relevant Zimmerman-Traxler transition state!

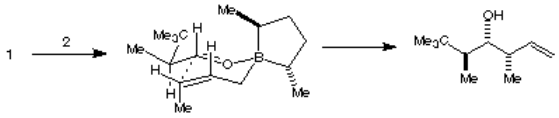


## Problem 94

Contributer: **David A. Evans**
Citation:

The reaction of 1 with 2 is a typical example of a double stereodifferentiating addition reaction. Determine whether this reaction is "matched" or mismatched, draw the transition state for the addition process that supports your conclusion, and provide the absolute stereochemictry of the addition product.



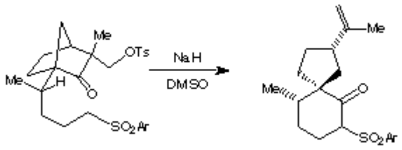


*transition state*
*stereogenic elements are "matched"*

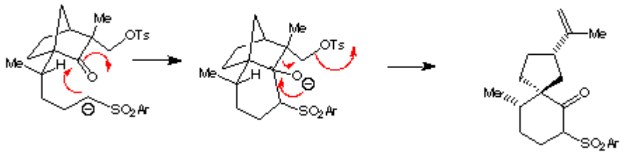
## Problem 95

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1978**, *43*, 1750

Magnus et al; have reported the base-induced transformation shown below (*J. Org. Chem* 1978, *43*, 1750).



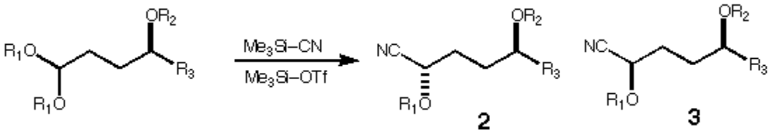
Provide a detailed mechanism for this transformation in the space below.



## Problem 97

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1991**, *113*, 3608

The development of stereocontrolled reactions is an important undertaking in organic synthesis. Recently, Molander and Haar disclosed "A Simple Method for Achieving High 1,4-Relative Asymmetric Induction in Carbonyl Reactions" (*JACS* **1991**, *13*, 3608). Their reaction is show below (eq 1).



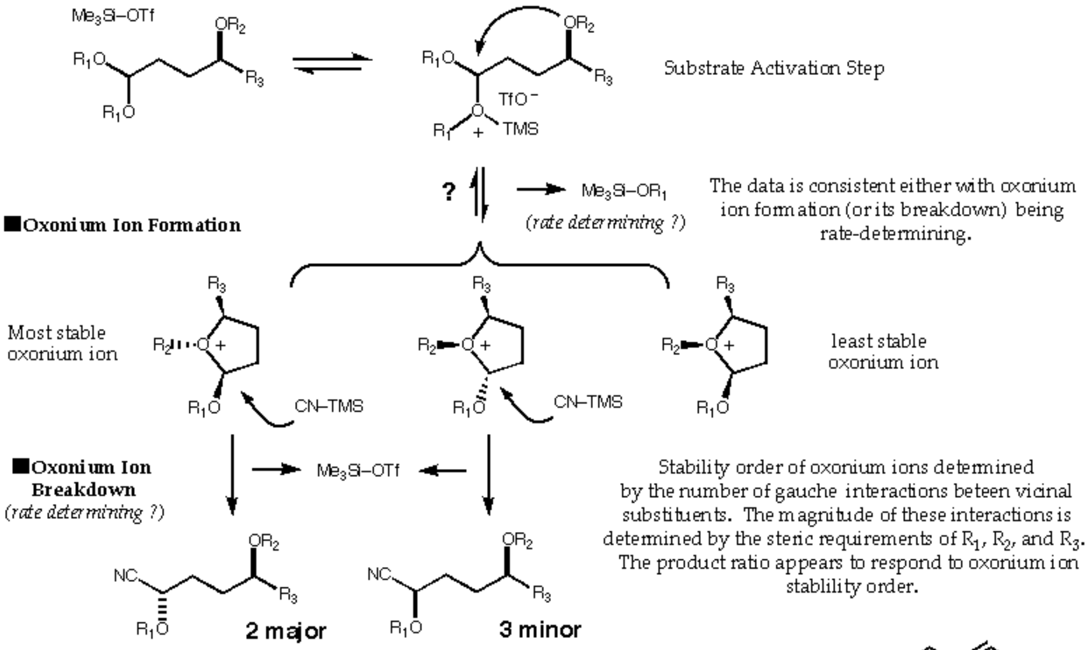
| $R_1$- | $R_2$- | $R_3$- | Ratio, **2** : **3** |
|---|---|---|---|
| Me- | Me- | Me- | 1.5 : 1 |
| *i*-Pr- | Me- | Me- | 5 : 1 |
| *i*-Pr- | Me- | *i*-Pr- | 15 : 1 |

**Conditions:** 10 mol % Trimethylsilyl triflate with one equiv each of TMSCN and acetal, -78 °C in $CH_2CL_2$.

■**The Nucleophile:** TMSCN is capable of undergoing rapid 1,2-silatropic rearrangement. I suspect that the isonitrile tautomer is involved in the rate-determining breakdown of the intermediate oxonium ion.

$$Me_3Si-C\equiv N: \rightleftharpoons Me_3Si-N\equiv C:$$

■**Acetal Activation:**



Substrate Activation Step

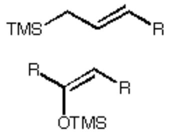
The data is consistent either with oxonium ion formation (or its breakdown) being rate-determining.

Most stable oxonium ion

least stable oxonium ion

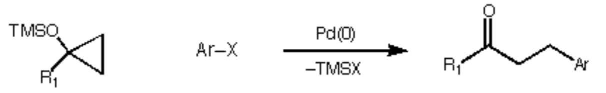
Stability order of oxonium ions determined by the number of gauche interactions beteen vicinal substituents. The magnitude of these interactions is determined by the steric requirements of $R_1$, $R_2$, and $R_3$. The product ratio appears to respond to oxonium ion stablility order.

■**Other Nucleophiles ??:** The nucleophile employed must be stable to the TMSOTf catalyst while maintaining sufficient nucleophilicity to participate in the reaction. Two typical candidates which might be considered are shown:
Can you think of others ?

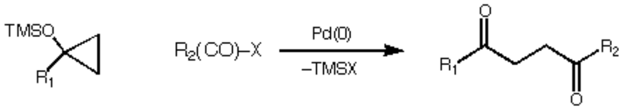


**Problem 98** Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1991**, *45*, 2809

Cyclopropanol derivatives are proving to be useful homoenolate anion equivalents, and over the last ten years metal-catalyzed reactions utilizing these intermediates in useful bond constructions have appeared. In 1988 the illustrated arylation reaction was reported, *JACS* **1988**, *110*, 3296, (eq 2) while more recently, Nakamura (*J.Org. Chem.* **1991**, *56*, 2809) reported a thorough study on the related acylation reactions (eq 3).



(2)

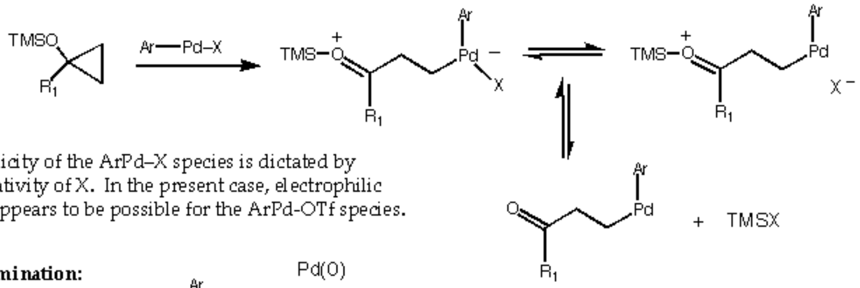


(3)

**Part A.** Write out the probable steps, *in equation form*, for the Pd-catalyzed transformation shown in eq 2.

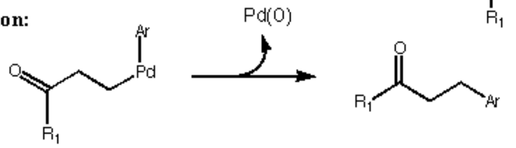
**Part B.** There appear to be some definite requirements for the Ar–X reacting partner in the arylation. For example, these reactions afford excellent yields of the desired product when aryl triflates are employed. On the other hand, aryl iodides fail to provide the desired product. Based on the mechanism which you have provided in Part A, speculate why aryl triflates, but not the analogous iodides, are required for coupling.

- **Oxidative Addition:** $\text{Ar—X} \xrightarrow{\text{Pd(0)}} \text{Ar—Pd–X}$ This step will take place for X = I, Br, or O–triflate
- **Electrophilic Addtion to Cyclopropyl Ring:**



The electrophilicity of the ArPd–X species is dictated by the electronegativity of X. In the present case, electrophilic addition only appears to be possible for the ArPd-OTf species.

- **Reductive Elimination:**



**Problem 102** Contributer: **David A. Evans**
Citation: *Organic Lett.* **2002**, *4*, 3179-3182

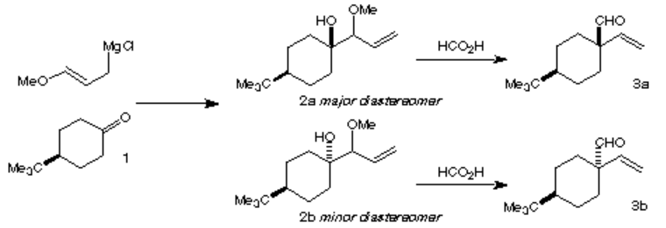
Consult the cited reference for an answer to this question

**Problem 103** Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **2003**, *44*, 1129-1132

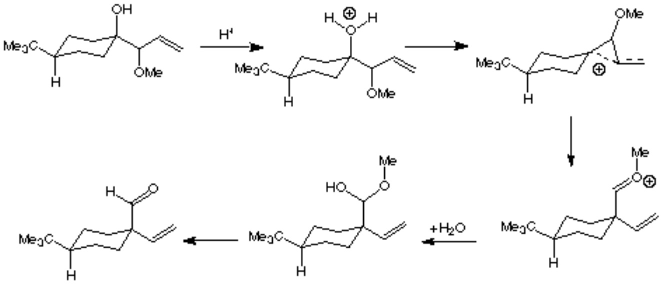
Consult the cited reference for an answer to this question

**Problem 104** Contributer: **David A. Evans**
Citation: *Evans, Unpublished Results*

The indicated allylmetal nucleophile adds regioselectively to the indicated cyclohexanone derivative 1 to afford the tertiary alcohols 2a and 2b having the indicated stereochemistry (Evans & Andrews, *Unpublished*, 1974). These adducts may be individually rearranged to the indicated aldehydes 3a and 3b with complete control of stereochemistry. This set of transformations readily provides access to functionalized quaternary centers.



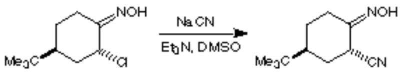
Provide a mechanism for the transformation of 2a into 3a that is consistent with the experimental observations. Where appropriate, provide three-dimensional drawings to reinforce your answer.



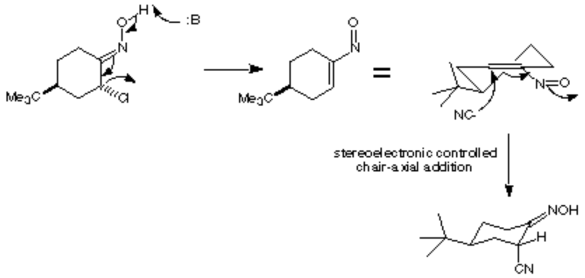
## Problem 110

Contributer: **David A. Evans**
Citation:

The indicated transformation occurs with apparent retenton of stereochemistry.



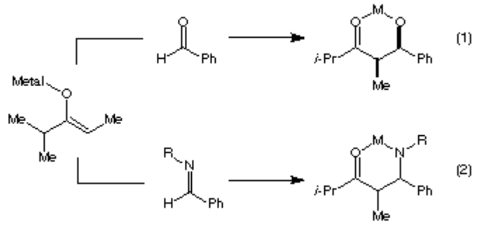
In the space below, provide an explanation for the mechanism and stereochemical outcome of this transformation.



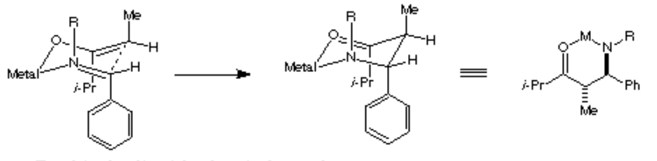
## Problem 111

Contributer: **David A. Evans**
Citation:

The Zimmerman-Traxler transition state nicely correlates starting enolate geometry and product aldol stereochemistry. This point is illustrated in equation 1 below in the correlation of the (Z) enolate geometry with the syn aldol product stereochemistry. The intent of this question is to have you ponder the related addition to the illustrated imine (eq 2).



In the space below, draw the Zimmerman-Traxler transition state for the "imine-aldol" process (eq 2) and illustrate the predicted stereochemical outcome of the addition reaction. Assume that the imine geometry cannot isomerize under the reaction conditions.

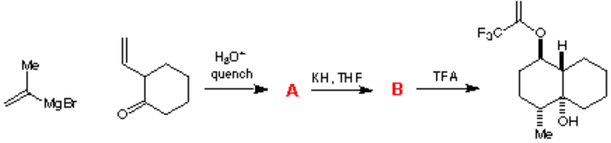


*Phenyl ring forced in axial conformation because of Zimmerman-Traxler transition state (mutual activation by metal)*

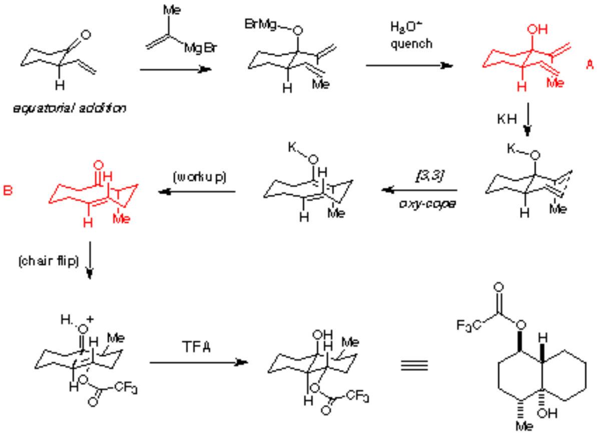
## Problem 114

Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **2001**, *42*, 3816

The following transformation was reported earlier this year by J. D. White and co-workers (*Tet Lett.* 2001, 42, 3816.). From your knowledge of the chemistry involved, provide a mechanism for the indicated transformation which is consistant with the observed product stereochemistry.



TFA = trifluoroacetic acid

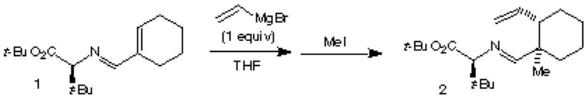


*equatorial addition*

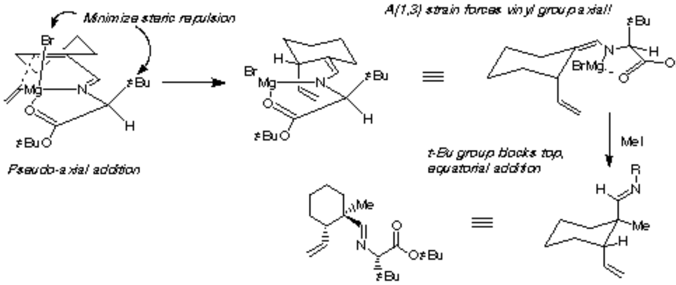
## Problem 115

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2001**

During their investigations toward a total synthesis of Nodulisporic Acid A, Smith and co-workers (Smith *Org. Lett.* 2001, ASAP) attempted a diastereoselective addition sequence based on the precedent of Koga (Koga, *Tet* 1981, 37, 3951.).



Part A. Provide a mechanism for the transformation of 1 to 2 as reported by Koga (shown below). Be sure your mechanism accounts for the observed stereochemisty.



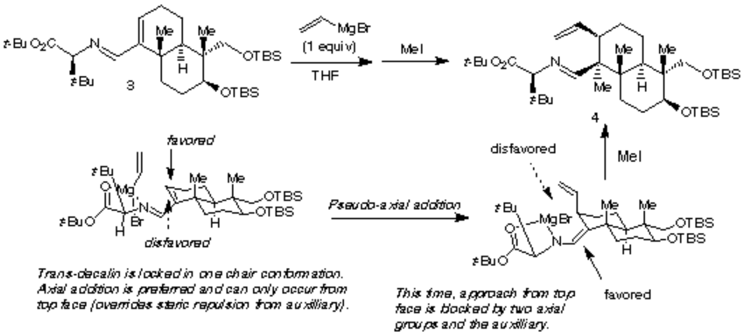
*Minimize steric repulsion*

*A(1,3) strain forces vinyl group axial!*

*Pseudo-axial addition*

*t-Bu group blocks top, equatorial addition*

Part B. While attempting to effect an analogous transformation on decalin 3, Smith and co-workers were quite suprised that *cis* diastereomer 4 was obtained. Provide a rationale for the divergent stereochemical outcome.



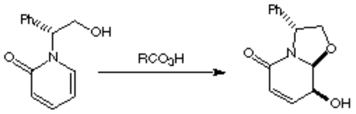
*Trans-decalin is locked in one chair conformation. Axial addition is preferred and can only occur from top face (overrides steric repulsion from auxilliary).*

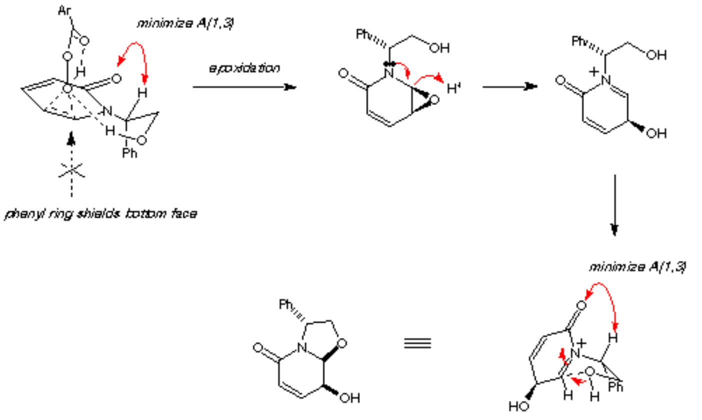
*This time, approach from top face is blocked by two axial groups and the auxilliary.*

## Problem 125

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2001**, *3*, 3257-3260

The following reaction was recently reported by Amat and co-workers (*Org. Lett.* 2001, 3, 3257-3260). Provide a mechanism for the this transformation which is consistent with the product stereochemistry. Since stereochemical issues are at stake, carefully rendered 3-D conformational drawings should be incorporated into your answer.

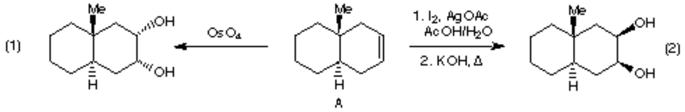




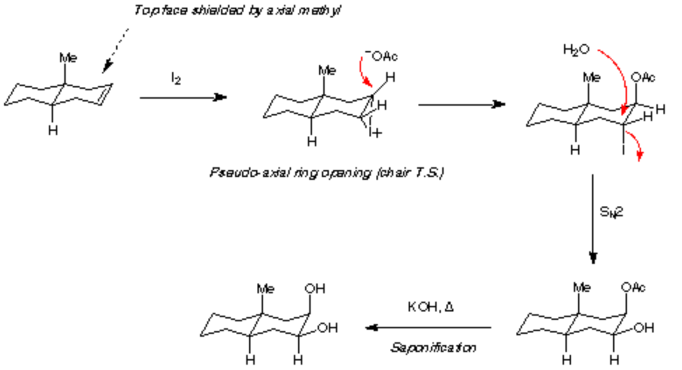
## Problem 127

Contributer: **David A. Evans**
Citation:

If an olefin such as A experiences a facial bias, one may count on steric effects to direct the course of a $OsO_4$ dihydroxylation to the *less hindered olefin diastereoface* (eq 1). Strategically, it is limportant to be able access the other stereochemical option: dihydroxylation from the *more hindered olefin diastereoface*. This stereochemical option may be implemented through the reaction summarized in equation 2. This reaction has been referred to as the Prevost-Winstein-Woodward dihydroxylation.



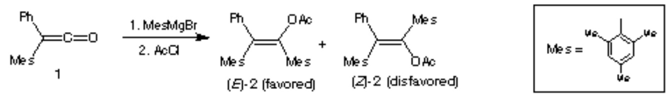
Provide a mechanism for the reaction illustrated in eq 2 in the space below. Since stereochemical issues are at stake, carefully rendered 3-D conformational drawings should be incorporated into your answer.



## Problem 133

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1996**, *118*, 12580

Rappoport has recently reported the transformation illustrated below (*JACS* 1996, *118*, 12580). The kinetic stereochemical outcome of this reaction is superficially unanticipated in that the Grignard reagent adds to ketene 1 from the "more hindered" carbonyl π-face. This value judgement evolves from the assumption that the *mesityl substituent is more sterically demanding than the phenyl substituent*.



(*E*)-2 (favored) (*Z*)-2 (disfavored)

(*E*/*Z*) = 3:1 (kinetic ratio)

Provide a rationalization for this "contrasteric" ketene addition.

We start by analyzing the conformation of the ketene.

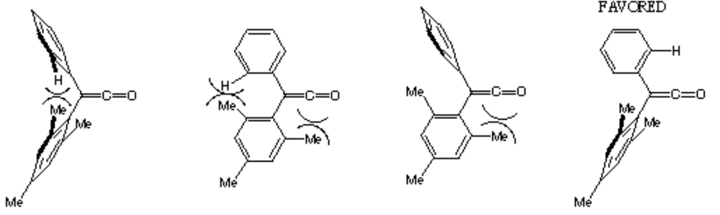
The all out-of-plane orientation has a steric clash between ortho substituents and also lacks any resonance stabilization from the phenyl groups

The all in-plane orientation of the aryl groups results in a very unfavorable clash between ortho groups

An in-plane orientation of the mesityl group has an unfavorable interaction between the methyl group and the ketene carbon

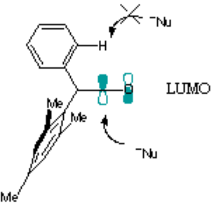
The in-plane orientation of the phenyl group provides some resonance stabilization and has no major steric clashes

FAVORED



Now we analyze the addition.

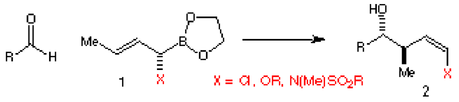
The LUMO of the ketene is in the plane of the substituents. Attack from the face syn to the phenyl group is blocked by the ortho hydrogen. Attack from the face syn to the mesityl is open because the mesityl group is out-of-plane.



## Problem 134

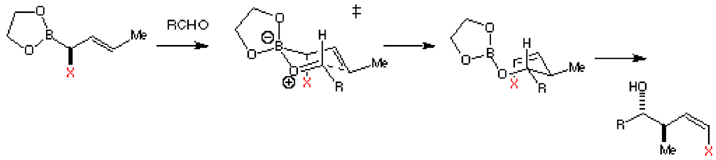
Contributer: **David A. Evans**
Citation: *Eur, J. Chem.* **2001**, 323

A recent paper by Hoffmann (*Eur. J. Org. Chem.* 2001, 323) highlights important advances made by this laboratory over the years in enantioselective aldehyde allylboration. A typical reaction developed by Hoffmann is illustrated below. In this case the enantiopure allylboronate 1 is transformed into the *anti* adduct 2 with high selectivities. The absolute stereochemical relationships of 1 and 2 are as illustrated.



Anti/syn diastereoselection > 15:1
enantioselection > 95%

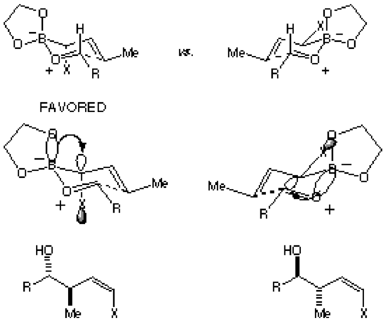
Part A. Draw the obligatory transition state for this transformation below. A carefully rendered three dimensional illustration is requested.



Part B. Identify those hyperconjugative effects, if any, that might be involved in transition state stabilization.

The complex undergoing allyl addition to the aldehyde prefers to have the R group of the aldehyde equatorial. This leaves two options for the position of the X group in the transition state.

*In this conformation, the X group is axial and the axial B-O bond can donate into C-X σ*.*

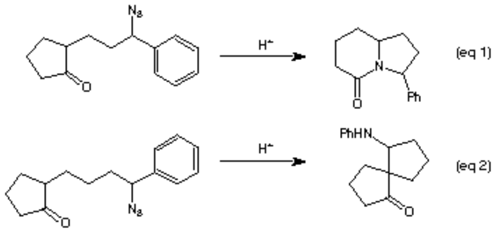


*In this conformation, the X group is equatorial and the B-O bond now capable of a hyperconjugative interaction is that of the carbonyl (a less electron rich B-O bond).*

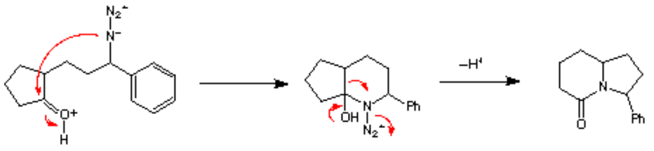
## Problem 141

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2001**, *66*, 886

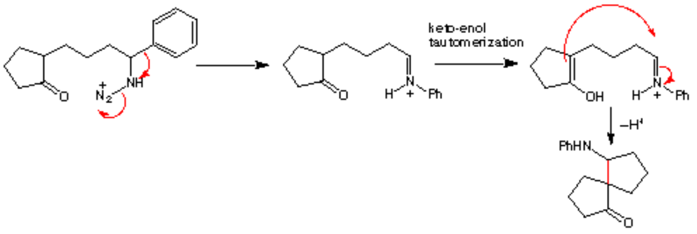
Aube has recently reported the transformations illustrated below (*J. Org. Chem.* 2001, 66, 886-889). In this study he has documented that the observed product is dependent on the tether length between the azide and carbonyl functional groups.



Part A. Provide a mechanism for the transformation illustrated in Eq 1.



Part B. Provide a mechanism for the transformation illustrated in Eq 2.



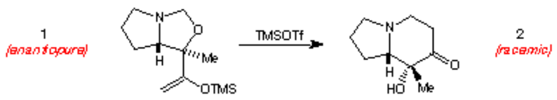
Part C. Briefly rationalize the difference in reactivity.

Cyclization of the azide onto the ketone in eq 1 forms a 6-membered ring and is therefore rapid. Cyclization of the azide onto the ketone in eq 2 would need to form a 7-membered ring, which is slow and allows the other reaction pathway to occur.

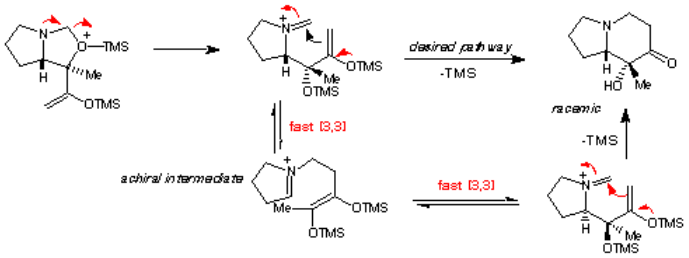
## Problem 142

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1992**, *57*, 1179

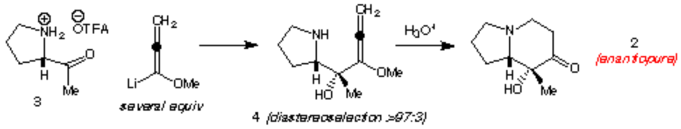
During the course of the Overman synthesis of pumilotoxin (*J. Org. Chem.* 1992, *57*, 1179) the indicated transformation was carried out with the expectation that the bicyclic ketone 2 would be enantiopure since the starting amine 1 was enantiomerically pure. Surprisingly, product 2 was obtained as a racemate.



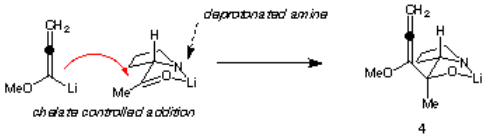
Part A. Provide a mechanism for this transformation that accounts for the illustrated stereochemical outcome.



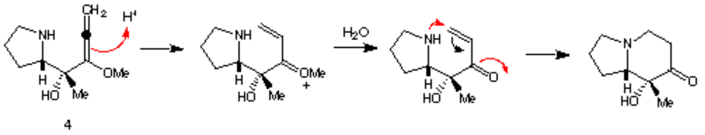
The revised synthesis of enantiomerically pure 2 is illustrated below (*J. Org. Chem.* 1992, *57*, 1179). Addition of 3 to several equivalents of the illustrated allenyllithium reagent afforded carbonyl adduct 4 as a single diastereomer. This intermediate was then transformed into enantiopure 2 under acidic conditions.



Part B. Provide an explanation for the high level of stereocontrol that is observed in the carbonyl addition step. A three dimensional drawing of the carbonyl addition transition state is requested in conjunction with this answer.



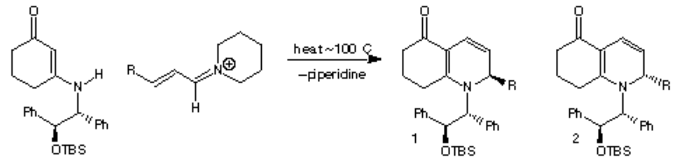
Part C. Provide a mechanism for the transformation of 4 to 2.



## Problem 143

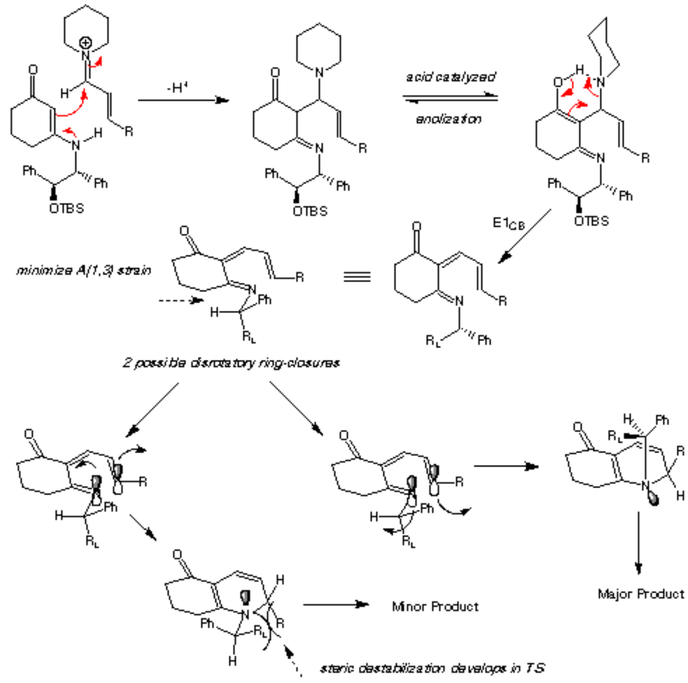
Contributer: **David A. Evans**
Citation: *Organic Lett.* **2000**, *2*, 1161

Hsung and co-workers have recently reported the diastereoselective reaction shown below (*Org. Lett.* 2000, 2, 1161). While there is mechanistic ambiguity associated with this process, the authors have suggested that a pericyclic process is involved in the stereochemistry-determining step, an assumption that is consistent with the sense of asymmetric induction observed in the reaction.



diastereoselection 1 : 2 >10:1

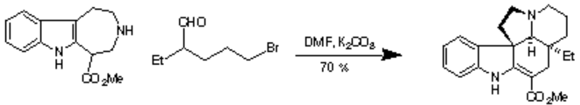
Provide a concise mechanism for this reaction in the space below. Please rationalize the observed sense of asymmetric induction.



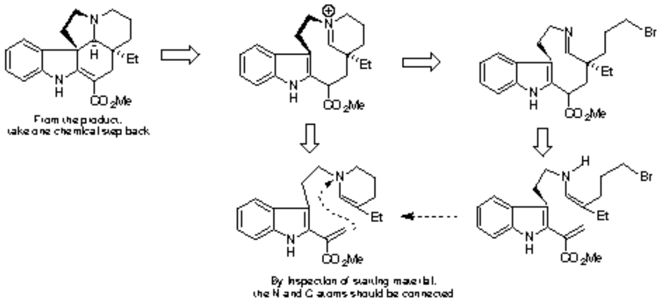
## Problem 145

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1978**, *43*, 3705

Martin Kuhne has described a biomimetic approach to the construction of the aspidosperma alkaloid skeleton (*J. Org. Chem.* 1978, *43*, 3705). One of the reactions developed in his laboratory is illustrated below.

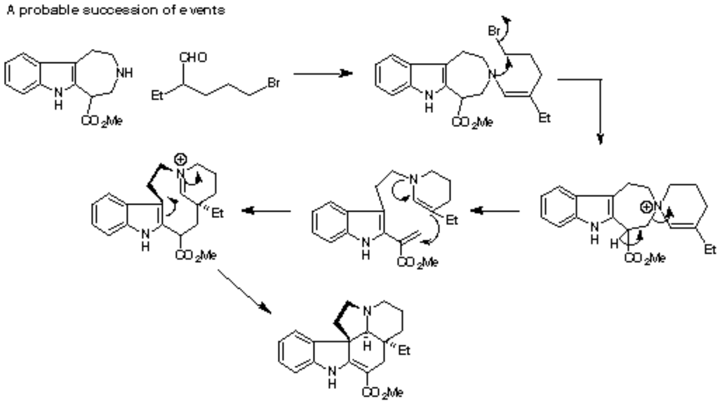


Provide a detailed mechanism for the illustrated transformation.



Et
CO2Me
Br
From the product, take one chemical step back
By inspection of starting material, the N and C atoms should be connected

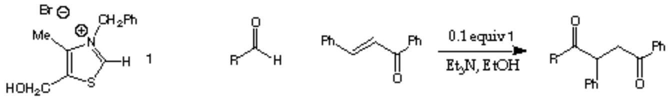
A probable succession of events



## Problem 149

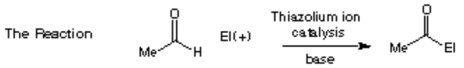
Contributer: **David A. Evans**
Citation: *Org. Reactions* **1991**, *40*, 407

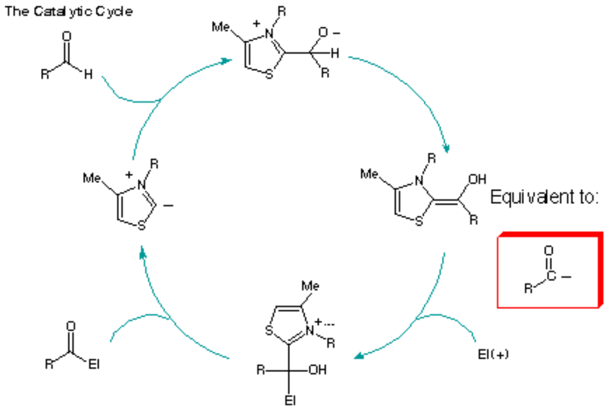
Stetter and coworkers (*Org. Reactions* 1991, *40*, 407) have developed the use of thiazolium salts for the coupling of aldehydes and unsaturated ketones. A typical transformation is illustrated below. The catalyst for this reaction is the thiazolium salt 1.



Provide a concise mechanism for this reaction in the space below.

*Aldehyde-Electrophile Coupling by Thiazolium Salts*

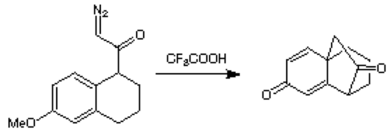




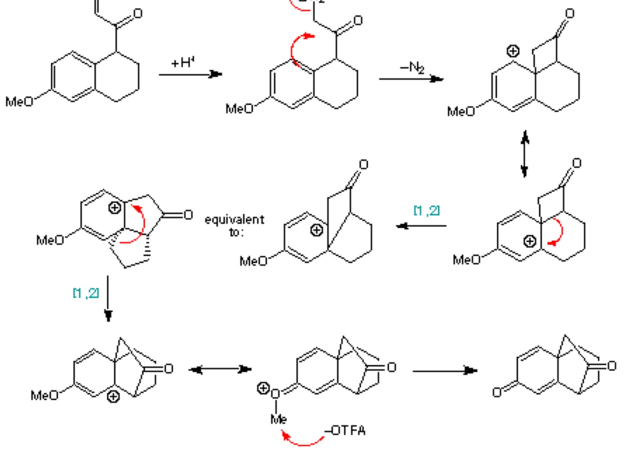
## Problem 150

Contributer: **David A. Evans**
Citation:

Provide a concise mechanism for the indicated reaction in the space below.



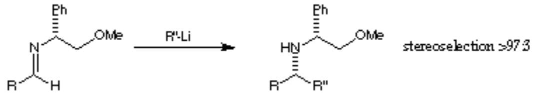
The Answer



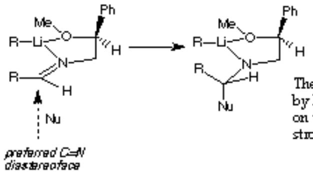
## Problem 151

Contributer: **David A. Evans**
Citation: *Chem. Lett.* **1991**, 1555

The following stereoselective transformation has been reported by Fujisawa (*Chem Lett.* 1991, 1555). Given the structure of the product, rationalize the stereochemical outcome of the process.



The rationalization ?

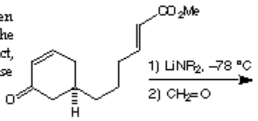


The stereochemical outcome of this reaction has been rationalized by Fujisawa through the chelate-organized imine complex shown on the left. In this study diastereoface selectivity was noted to be strongly dependant on the nature of the organometallic reagent.

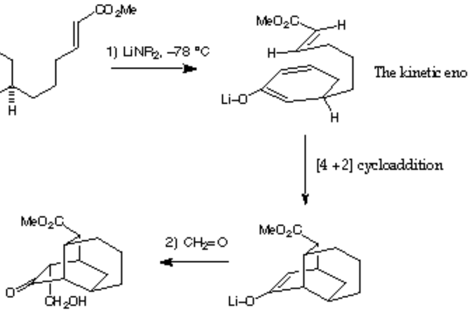
## Problem 156

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1994**, *59*, 6008

Here is an interesting transformation that has been reported by Ihara (*JOC* 1994, *59*, 6008). Given the partial structural information for the product, predict its structure and provide a concise mechanism for this process.



The Product
Here are some clues
A) No C=Cs in the product
B) CH$_2$=O incorporated



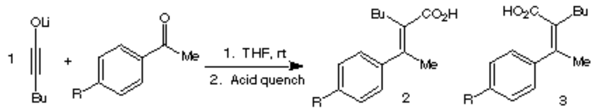
The kinetic enolate is formed

The product enolate is quenched by the enolate from the sterically least hindered diastereoface

## Problem 160

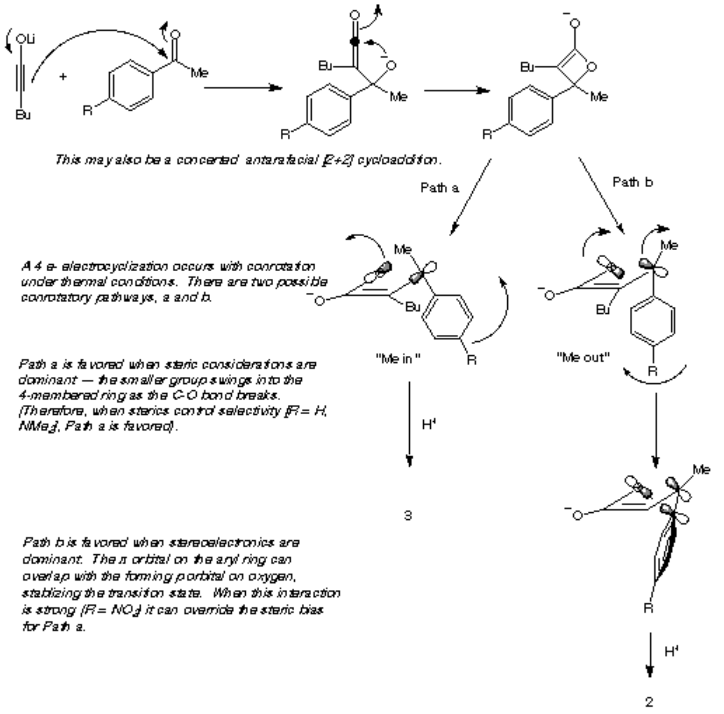
Contributer: **David A. Evans**
Citation:

The acetylene alkoxide (ynolate) 1 reacts with the indicated para-substituted acetophenones to give the (*E*) and (*Z*) unsaturated acids 2 and 3. The interesting observation is that the (*E*):(*Z*) product ratio strongly depends on the substituent on the aromatic ring.



| R | Ratio (2:3) |
|---|---|
| $Me_2N$ | >99:1 |
| H | 86:14 |
| $NO_2$ | 40:60 |

Provide a mechanism for the overall transformation illustrated below that accounts for the change in product stereochemistry with the change in acetophenone substituent R. Address stereochemical and stereoelectronic issues where appropriate. Classify all pericyclic reactions should they intervene.



*This may also be a concerted antarafacial [2+2] cycloaddition.*

*A 4 e- electrocyclization occurs with conrotation under thermal conditions. There are two possible conrotatory pathways, a and b.*

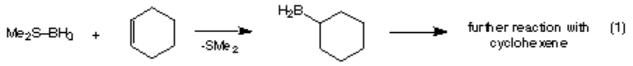
*Path a is favored when steric considerations are dominant — the smaller group swings into the 4-membered ring as the C-O bond breaks. (Therefore, when sterics control selectivity [R = H, NMe$_2$], Path a is favored).*

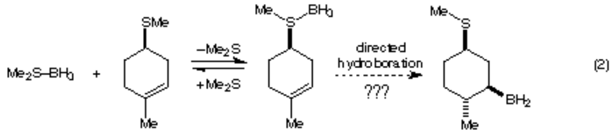
*Path b is favored when stereoelectronics are dominant. The π orbital on the aryl ring can overlap with the forming p orbital on oxygen, stabilizing the transition state. When this interaction is strong (R = NO$_2$) it can override the steric bias for Path a.*

## Problem 163

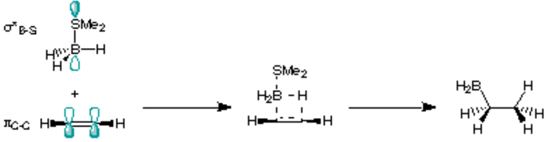
Contributer: **David A. Evans**
Citation:

The following is an idea that has been proposed to you by a fellow student. The proposal is based on the fact that borane–methyl sulfide complex is an effective hydroboration reagent (eq 1). It is proposed that allylic sulfides such as that illustrated below should be capable of "directing" the hydroboration process from this substituent through the borane-substrate complex.





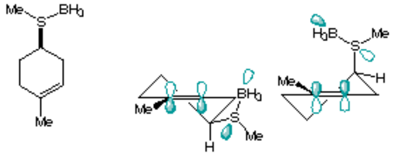
Part A. In order to begin your critique, you must possess a good working knowledge of the details of the hydroboration of olefins with borane–methyl sulfide. Provide a clear depiction of the transition state for the hydroboration process using ethylene as the olefinic substrate and borane–methyl sulfide as the hydroborating agent.



*4-center transition state*

*Note the anti disposition of the sulfide leaving group and the attacking olefin.*

Part B. Now, based on your knowledge of the hydroboration reaction and the principles learned thus far in Chem 206, critique the idea proposed in Eq 2. You must concisely state the logic upon which you base your assessment. *Pictures speak a thousand words.*

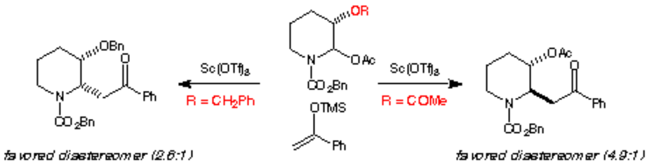


*In either half-chair, it is impossible to achieve π C-C overlap with σ* B-S — which is required for intramolecular delivery of $BH_3$. This violates the endocyclic restriction test and, therefore, attempts to use allylic sulfides to direct a hydroboration are doomed to failure.*

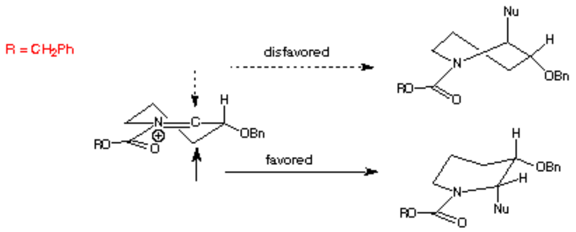
## Problem 165

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2001**, *66*, 809-823

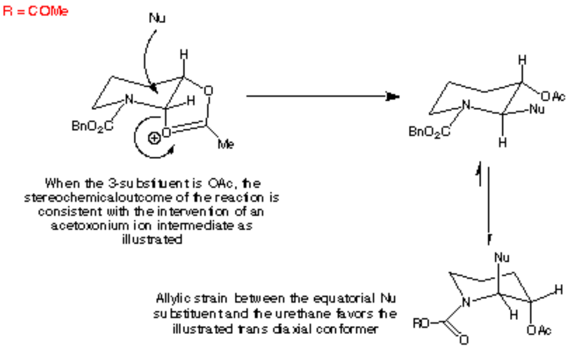
Kobayashi has recently reported the illustrated diastereoselective addition reactions (*J. Org. Chem.* 2001, 66, 809-823). This study reports that reaction diastereoselection may be controlled by the nature of the oxygen substituent at the 3-position of the piperidine ring.



Provide an explanation for these observations in the space below.



The cis product is favored on stereoelectronic grounds



When the 3-substituent is OAc, the stereochemical outcome of the reaction is consistent with the intervention of an acetoxonium ion intermediate as illustrated

Allylic strain between the equatorial Nu substituent and the urethane favors the illustrated trans diaxial conformer

## Problem 170

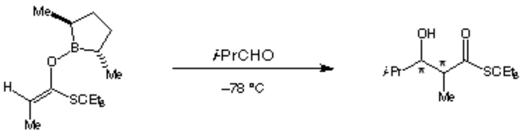
Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2000**, *65*, 8564

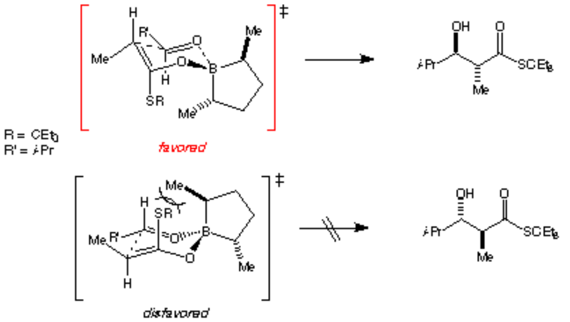
Consult the cited reference for an answer to this question

## Problem 173

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1986**, 8297

Provide a clear depiction of the transition state which predicts the product stereochemistry at the starred (*) carbon atoms (Masamune, *JACS*, **1986**, 8279).

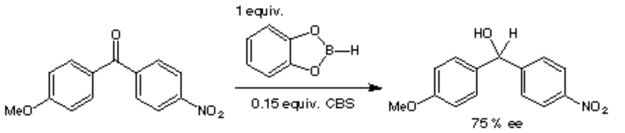




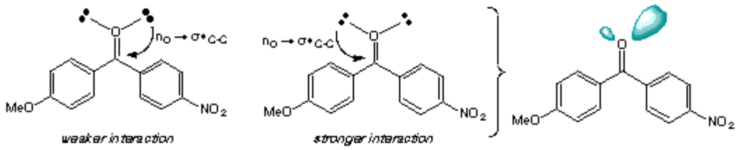
## Problem 174

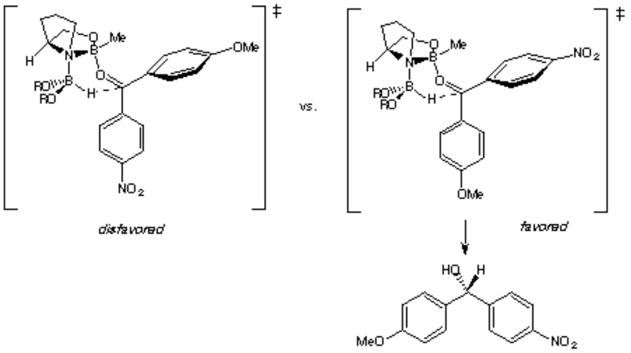
Contributer: **David A. Evans**
Citation: *Angew. Chem.* **1998**, 1987

Corey's CBS catalyst for ketone reduction often delivers high yields of enanticenriched secondary alcohols (*ACIE*, 1998, 1987). Provide a clear clear illustration of the transition state which predicts the absolute stereochemistry of the product obtained in the illustrated reaction. Include an explanation of why the reduction of this practically symmetric ketone is selective.



*The availability of ketone lone pairs must be considered. Because the antiperiplanar C-C sigma bonds have differing electron density, the ketone lone pairs will be anisotropic. The $n_O \rightarrow \sigma^*_{C\text{-}C}$ interaction with the electron rich C-C bond will be weak relative to the $n_O \rightarrow \sigma^*_{C\text{-}C}$ interaction with the electron deficient C-C bond. Complexation of the lone pair anti to the p-methoxy phenyl substituent will be favored.*

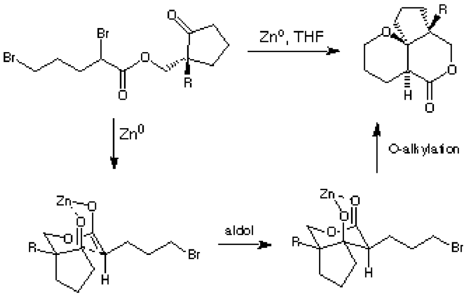




## Problem 179

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1989**, 1530

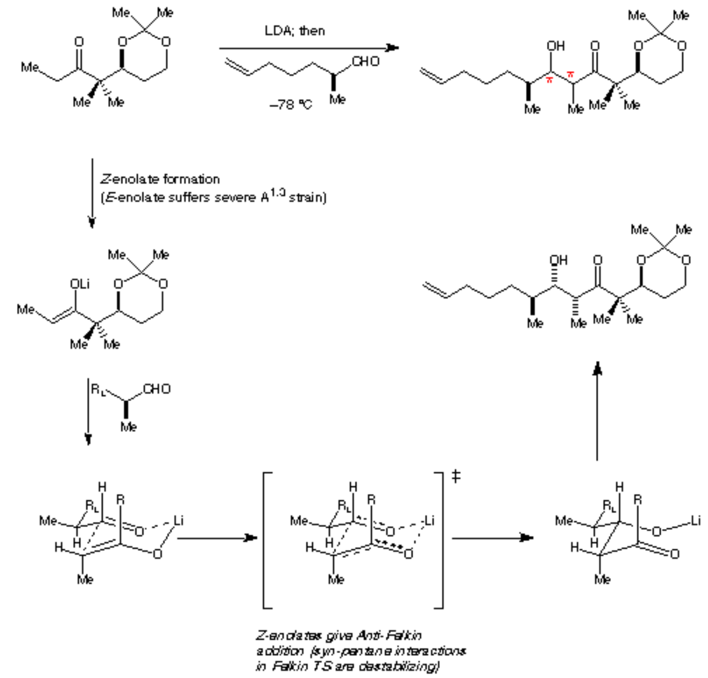
Provide a mechanism that accounts for observed stereochemistry of the illustrated transformation (Heathcock, *JACS*, 1989, 1530).



## Problem 180

Contributer: **David A. Evans**
Citation: *Angew. Chem.* **1997**, *36*, 523

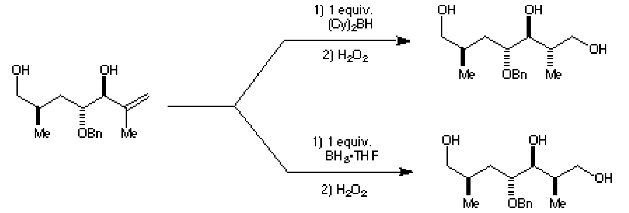
Provide a mechanism which clearly predicts the product stereochemistry at the starred (*) carbon atoms (Schinzer, *ACIEE*, 1997, 36, 523). Provide a clear depiction of the transition state to support your answer.



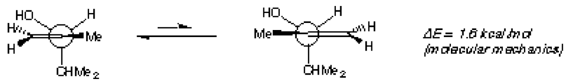
*Z-enolates give Anti-Felkin addition (syn-pentane interactions in Felkin TS are destabilizing)*

**Problem 182** Contributer: **David A. Evans**
Citation:

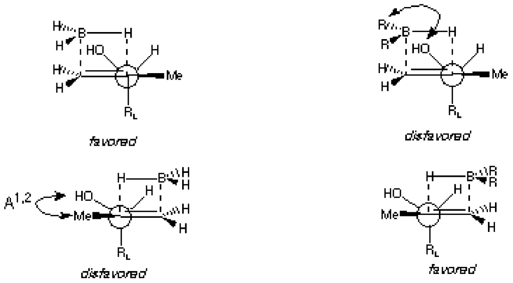
Provide clear three-dimensional depictions of the transition states for the following hydroborations. Specifically point out each factor responsible for the observed turnover in selecivity (Tatsuda, *TL*, 1991, 6015).



- *In the favored transition states, torsional interactions will be minimized, placing the large group ($R_L$) anti to the incoming reagent.*
- *Recall that for 1,2-disubstituted olefins, 1,2 allylic strain ($R_m$ = Me, OH) is dominant over 1,3 allylic strain:*

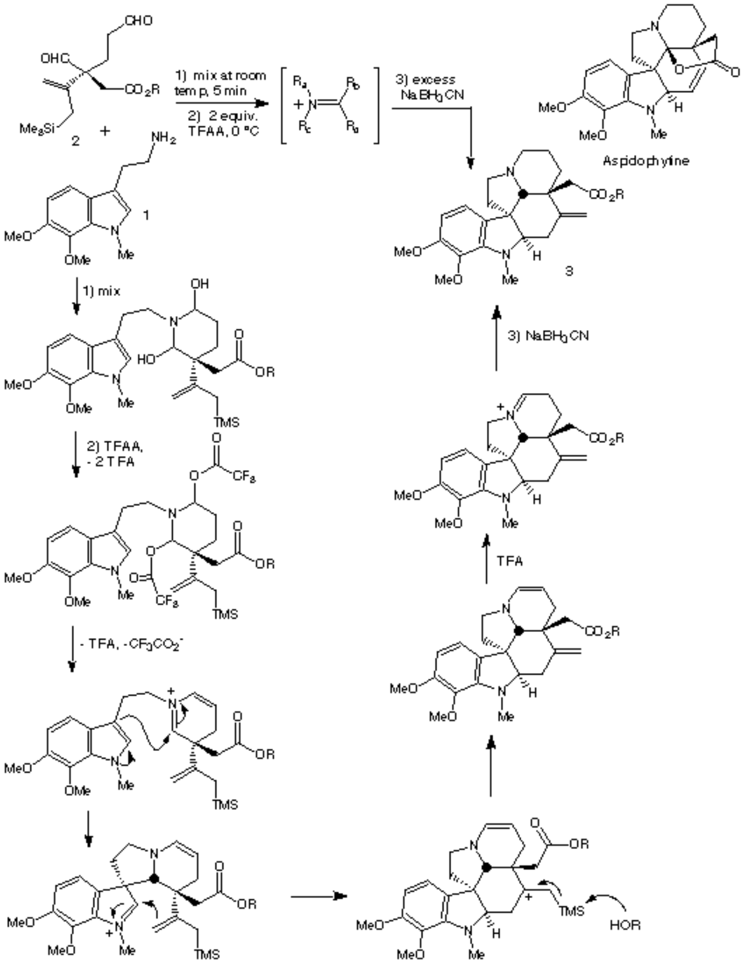


- *These features predict the product for the case of the small reagent $BH_3$·THF.*
- *For the more bulky (Cy)$_2$BH, the selectivity turns over because the dominant interaction now is that between the ligands on boron and the larger hydroxyl group. A 180° rotation releaves this interaction by replacing it with a smaller ligand - hydrogen interaction. This lower energy transition state leads to the observed product.*
- *For more discussion, see Houk, JACS, 1995, 9434 and references therein.*



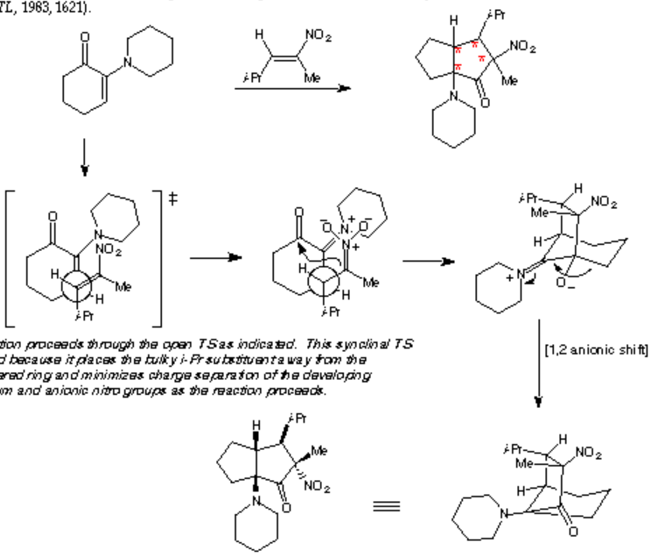
**Problem 185** Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1999**, *121*, 6771

During Corey's recent synthesis of Aspidophytine (*JACS* 1999, *121*, 6771), the pivotal intermediate 3 was assembled by the union of 1 and 2 under the specified conditions. Provide a mechanism for this single-pot transformation.



**Problem 188** Contributer: **David A. Evans**
Citation: *Tetrahedron Lett.* **1983**, 1621

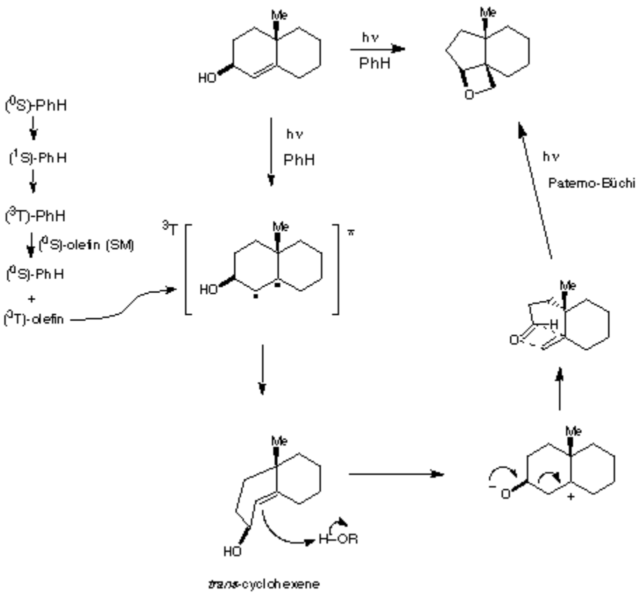
Provide a mechanism for the following reaction that predicts the stereochemistry at the starred (*) carbon atoms (Valentin, *TL*, 1983, 1621).



*The reaction proceeds through the open TS as indicated. This synclinal TS is favored because it places the bulky i-Pr substituent away from the 6-membered ring and minimizes charge separation of the developing ammonium and anionic nitro groups as the reaction proceeds.*

**Problem 190** Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1971**, 214

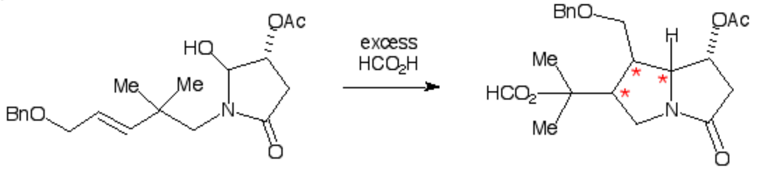
Provide a mechanism for the following transformation that explains the observed stereochemistry (Marshall, *JOC*, 1971, 214).



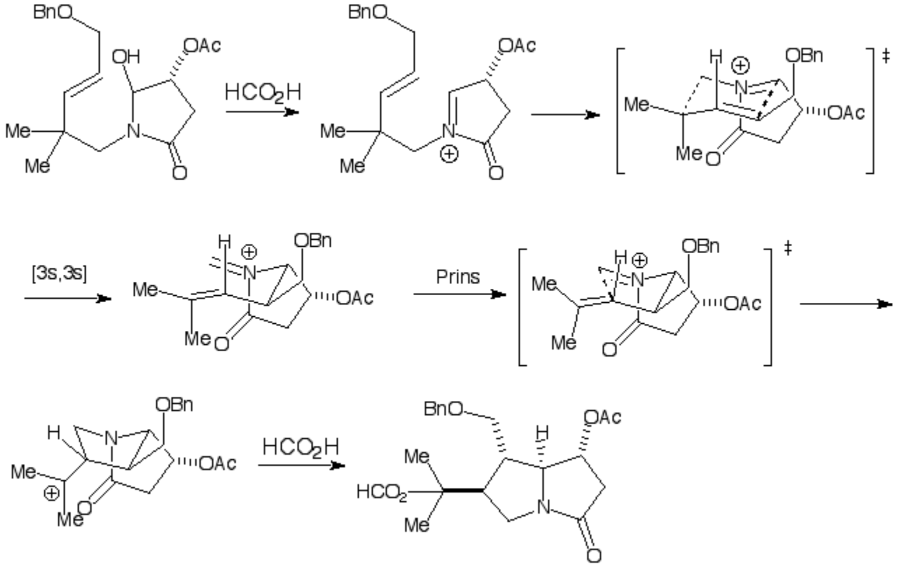
## Problem 193

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1985**, 235

Provide a mechanism for the indicated transformation that predicts the observed stereochemistry at the three starred (*) carbon atoms (*JOC*, **1985**, 235).



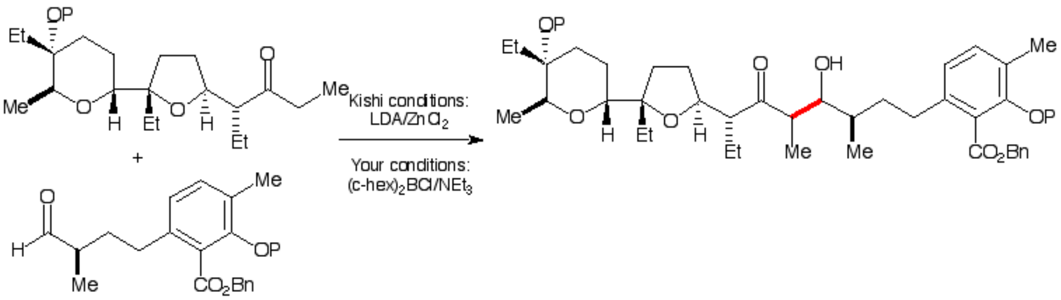
**Answer**



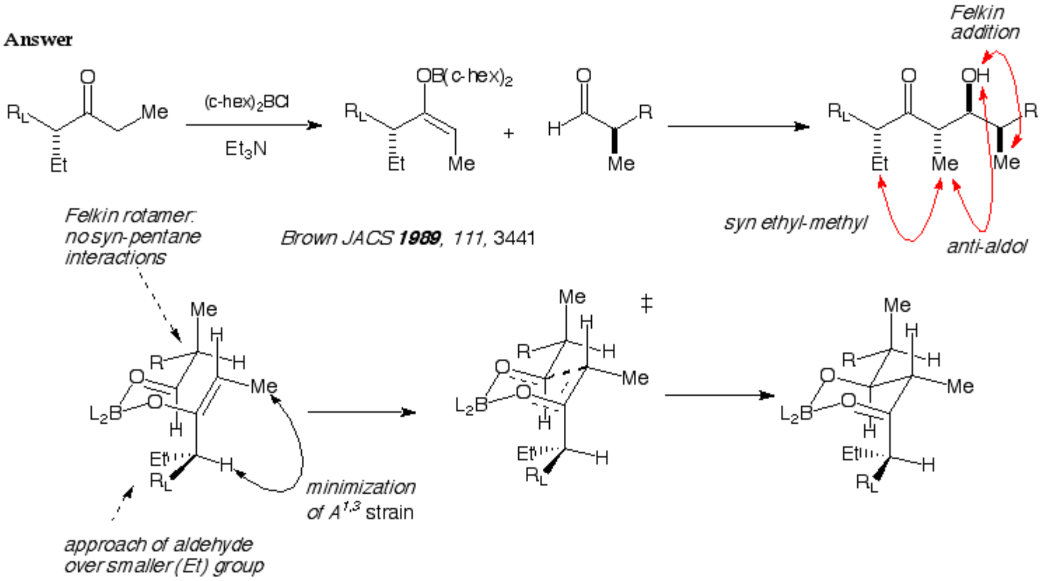
## Problem 194

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1978**, 2933

In the Kishi Lasalocid A synthesis, the illustrated aldol fragment coupling proceeded with only moderate stereoselectivity (*JACS*, **1978**, 2933). If you were planning this fragment coupling today, you would probably choose (c-hex)$_2$BCl / NEt$_3$ which would cleanly provide the (E) boron enolate (Brown *JACS* **1989**, *111*, 3441). What product stereochemistry would you expect from your reaction? Include a transition state drawing to support your answer. Point out the specific factors responsible for your predicted selectivity. Is your reaction a fully matched or partially matched aldol reaction?



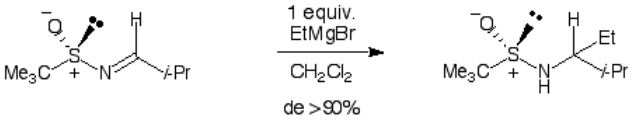
**Answer**


(c-hex)2BCl
Et3N
RL
Et
Me
OB(c-hex)2
+
H
R
Me
Felkin addition
OH
R
syn ethyl-methyl
anti-aldol
Brown JACS 1989, 111, 3441
Felkin rotamer: no syn-pentane interactions
Me
H
R
H
Me
L2B
O
O
H
Et
RL
H
minimization of A1,3 strain
approach of aldehyde over smaller (Et) group
‡

*The use of (c-hex)$_2$BCl and triethylamine will produce an E-enolate (Brown JACS **1989**, 111, 3441). This E-enolate will give an anti-aldol adduct because of a Zimmerman-Traxler transition state. E-enolates are Felkin selective nucleophiles, and the chiral enolate will give the syn ethyl-methyl across the carbonyl. The integrated transition state is depicted above. Note that A$^{1,3}$ strain is minimized in the E-enolate and that the aldehyde has adopted the Felkin-Ahn rotamer. This aldol reaction is fully matched because both the aldehyde and enolate facial selectivity are reinforcing in a Zimmerman-Traxler transition state.*

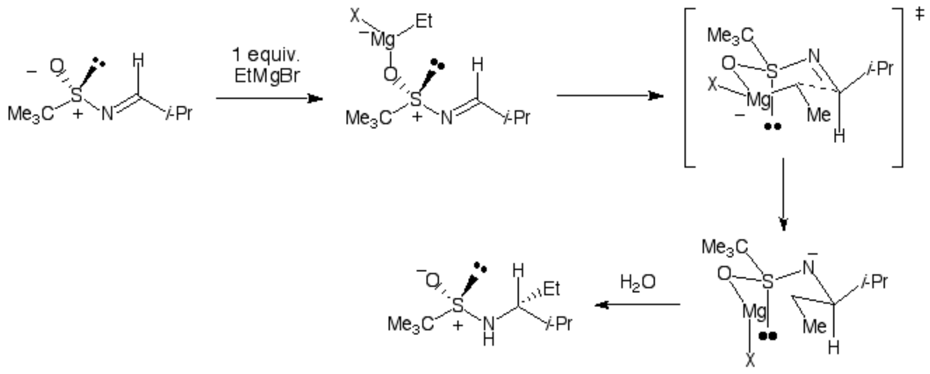
**Problem 196**
Contributer: **David A. Evans**
Citation: *Tetrahedron* **1999**, 8883

**Part A.** Provide a mechanism for the following reaction (*Tetrahedron*, **1999**, 8883). Include a clear transition state representation that predicts the major product diastereomer.



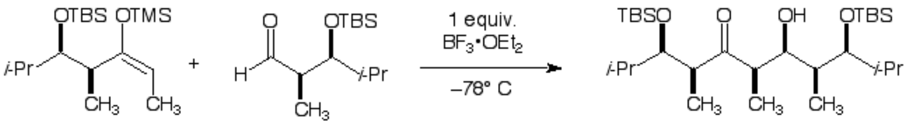
**Part B.** When the reaction is performed in diethyl ether or THF, the diastereoselectivity is significantly lowered. Propose an explanantion for this observation.

**Answer**

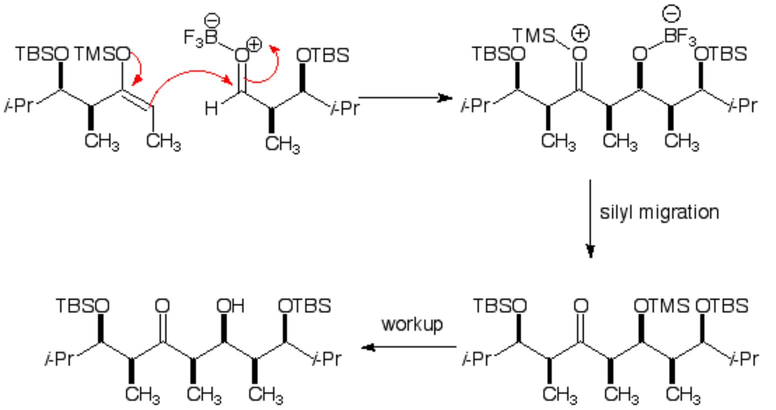


**Problem 197**
Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1995**, 9598

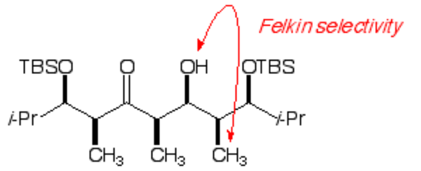
Provide a mechanism for the following monodentate Lewis acid promoted aldol reaction. Include a transition state representation, indicating the specific factors that are responsible for the observed selectivity (*JACS*, **1995**, 9598).



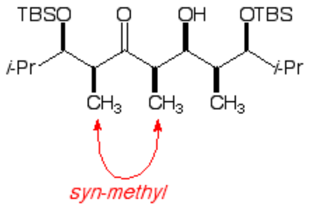
**Answer**



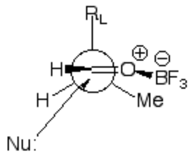
*Since this reaction does not proceed through a closed Zimmerman-Traxler transition state ($BF_3$•$OEt_2$ is a monodentate Lewis acid, not capable of coordinating 2 oxygen ligands), the mnemonic that E-enolates → anti products and Z-enolates → syn products does not apply. In this instance we consider the chiral elements of the aldehyde and the enolate separately.*



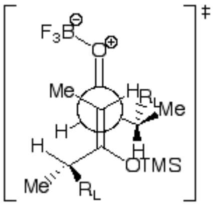
*The hydroxyl stereocenter is controlled by the facial selectivity of the chiral aldehyde. In this case, the product is the result of Felkin-Anh addition to the carbonyl.*

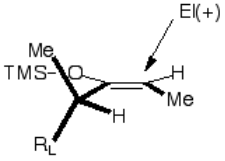


*The methyl stereocenter is controlled by the facial selectivity of the chiral enolate. In this case, we apply the Evans model for E-enolates. Minimization of $A^{1,3}$ strain gives the structure shown below. The aldehyde approaches from the top face.*



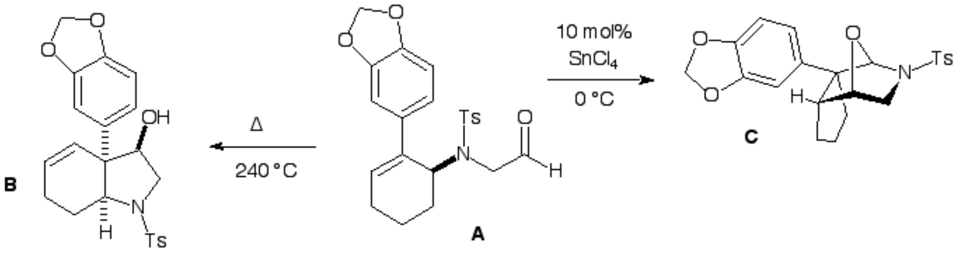
*TS incorporating each feature:*



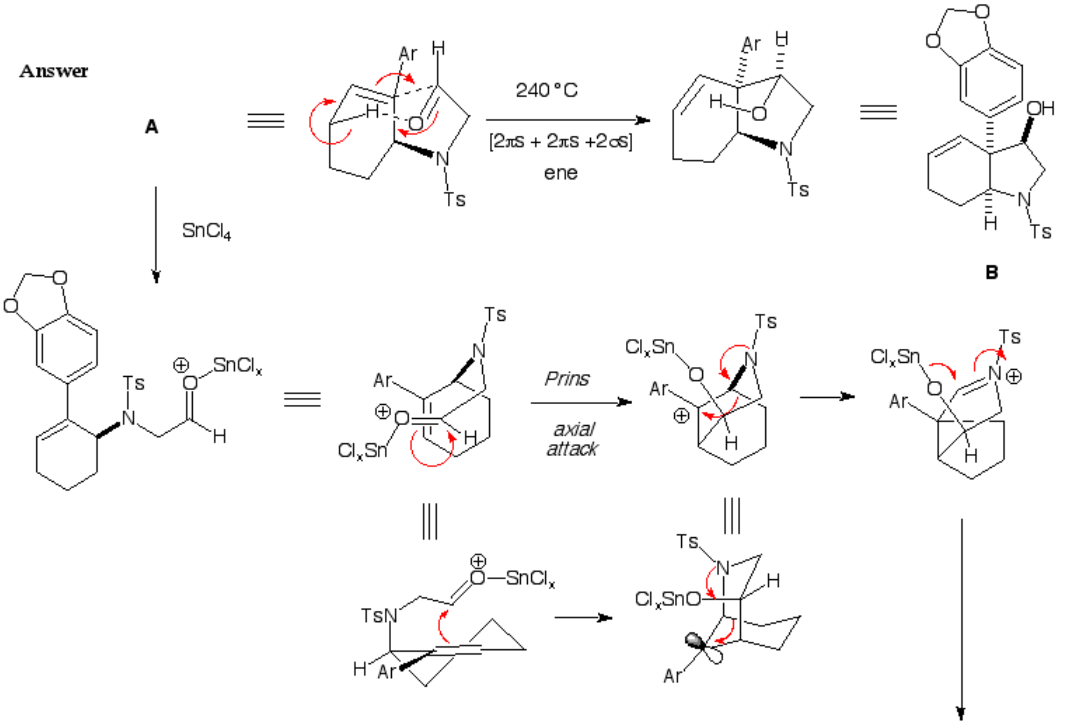


**Problem 203** Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1998**

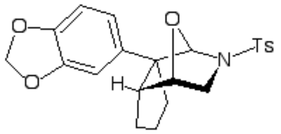
Provide mechanisms that account for the stereoselective formation of the products obtained by treatment of aldehyde **A** to the conditions shown below. Briefly comment on the difference in reactivity under the two sets of conditions (*JOC*, **1998**, 7586).



**Answer**

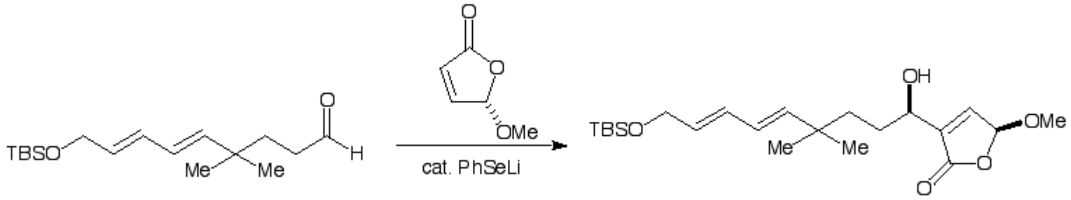


*Thermal conditions promote a concerted ene reaction. Under Lewis acidic conditions, a stepwise mechanism predominates where a Prins reaction leads to the stablized benzylic cation. Nitrogen assisted ring contraction leads to the iminium ion which is quenched by the alkoxide.*

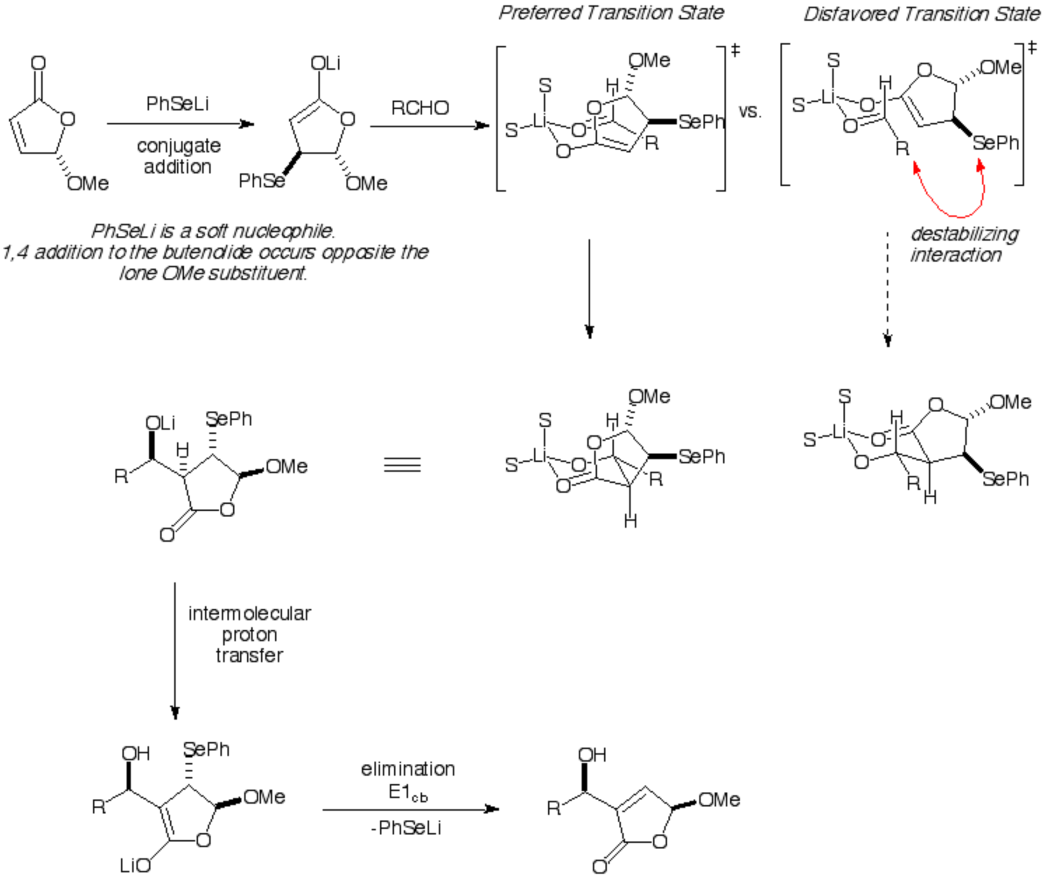

**C**

**Problem 204** Contributer: **David A. Evans**
Citation: *SynLett* **1999**, 1325

Provide a mechanism for the following reaction that explains the observed reaction diastereoselectivity (*Synlett*, **1999**, 1325). Be sure your mechanism accounts for the catalytic nature of PhSeLi.



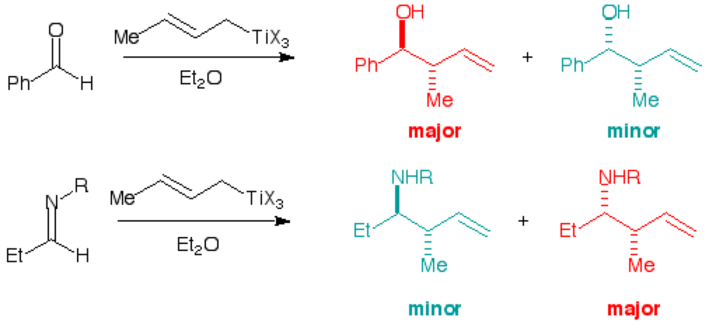
**Answer**



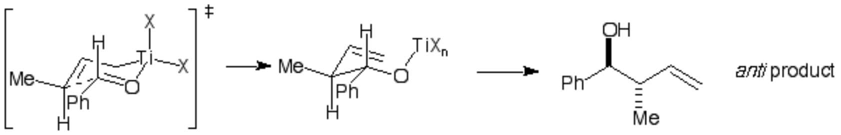
*PhSeLi is a soft nucleophile. 1,4 addition to the butenolide occurs opposite the lone OMe substituent.*

**Problem 205** Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1995**, 3881

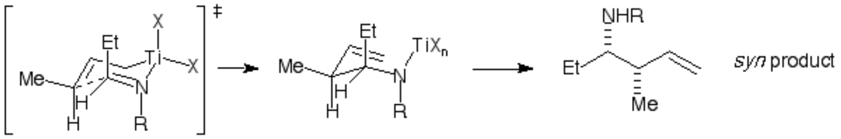
Crotyl titanium reagents have been developed for addition to C=O and C=N bonds (*J. Am. Chem. Soc.* **1995**, 3881 and *J. Org. Chem.* **1995**, 8136).



**Part A.** Provide an explanation, including clear 3D drawings of the transition states, which account for the divergent stereoselectivity observed in the addition reactions illustrated above.

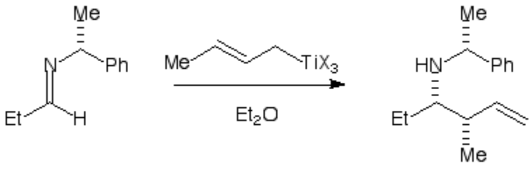


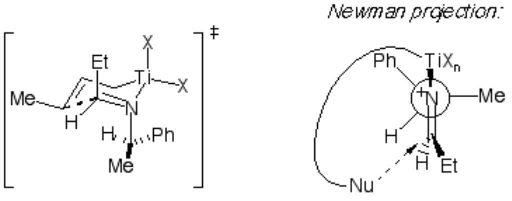
*In the Zimmerman-Traxler transition state, the aldehyde is oriented with the large substituent psuedo-equatorial.*



*The (E)-imine, by the nature of its geometry occupies a TS conformation in which the large substituent is psuedo-axial, leading to the syn product.*

**Part B.** The use of a chiral imine induces useful levels of asymmetric induction in this reaction. Provide an explanation, including a clear 3D drawing of the transition state, which accounts for the preferred production of the indicated diastereomer.

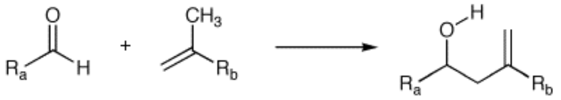




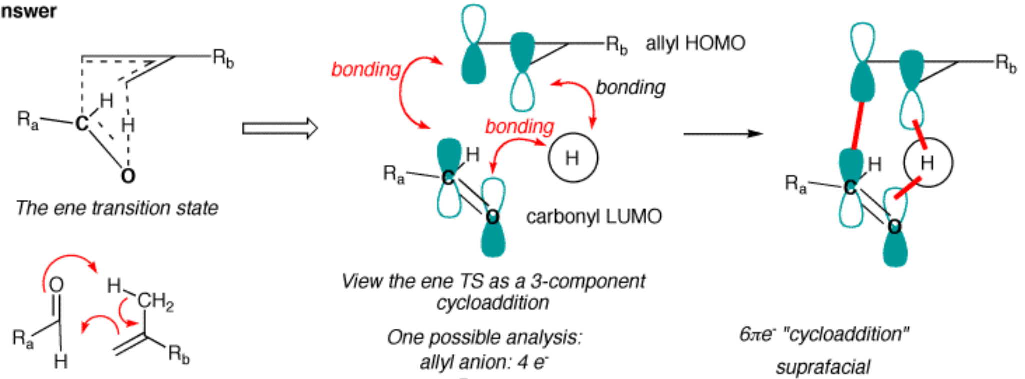
*Minimization of eclipsing interactions in the staggered TS (Houk), with the best donor (Me) orthogonal to the iminium N=C. (See Problem Set 5 Q#8 and class notes for a complete discussion).*

**Problem 210** Contributer: **David A. Evans**
Citation:

The carbonyl ene reaction is illustrated below. Using FMO analysis, evaluate the transition state of this reaction. Your answer should include: a transition state drawing; clear orbital depictions and HOMO-LUMO assignments; an indication of the number of electrons from each segment; and indication of whether the reaction is thermally allowed.



**Answer**



*The ene transition state*

*View the ene TS as a 3-component cycloaddition*

*One possible analysis:*
*allyl anion: 4 $e^-$*
*Proton*
*carbonyl: 2 $e^-$*

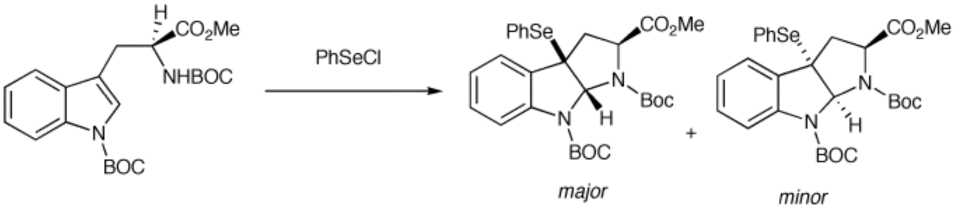
*[$2\pi s + 2\pi s + 2\sigma s$]*

*$6\pi e^-$ "cycloaddition"*
*suprafacial*
*thermally allowed*

## Problem 222

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1999**, *121*, 11953

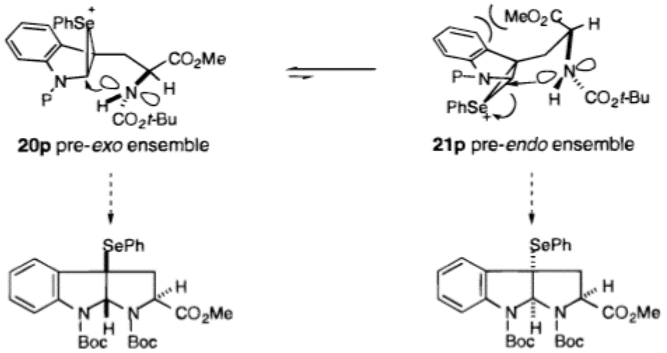
Provide a mechanism for the following reaction and explain the stereoselectivity. (Danishefsky, *JACS* **1999** 121, 11953)



*19:1 Diastereoselectivity*

**Answer:**

The stereochemistry-determining step is the attack on the bridged cationic selenium intermediate **22p** and **21p** as illustrated below. Developing non-bonging interactions disfavor the cyclization of **21p**.



**20p** pre-*exo* ensemble

**21p** pre-*endo* ensemble

**20** (*exo* product)

**21** (*endo* product)

## Problem 225

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1983**, *48*, 2685

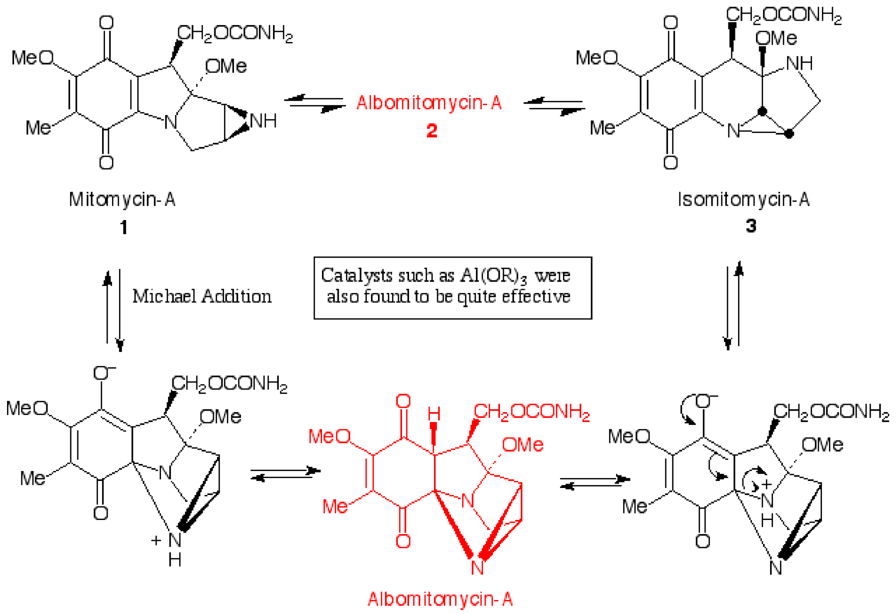
Consult the cited reference for an answer to this question

## Problem 226

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1987**, *109*, 7881

The Fukuyama synthesis of the mitomycins (*JACS* **1987**, *109*, 7881) proceeds through the intriguing rearrangement shown below. This transformation, which was first documented by Kono and co-workers (*JACS* **1987**, *109*, 7224) occurs upon dissolving either **1**, **2**, or **3** in methanol over a two-day period. The equilibrium mixture, which may be approached from any one of the three constituents, favors the mitomycin skeleton (Ca 90%).

Draw a detailed mechanism for the conversion of **3** ⇒ **2** ⇒ **1** and clearly identify the structure of albomitomycin-A.



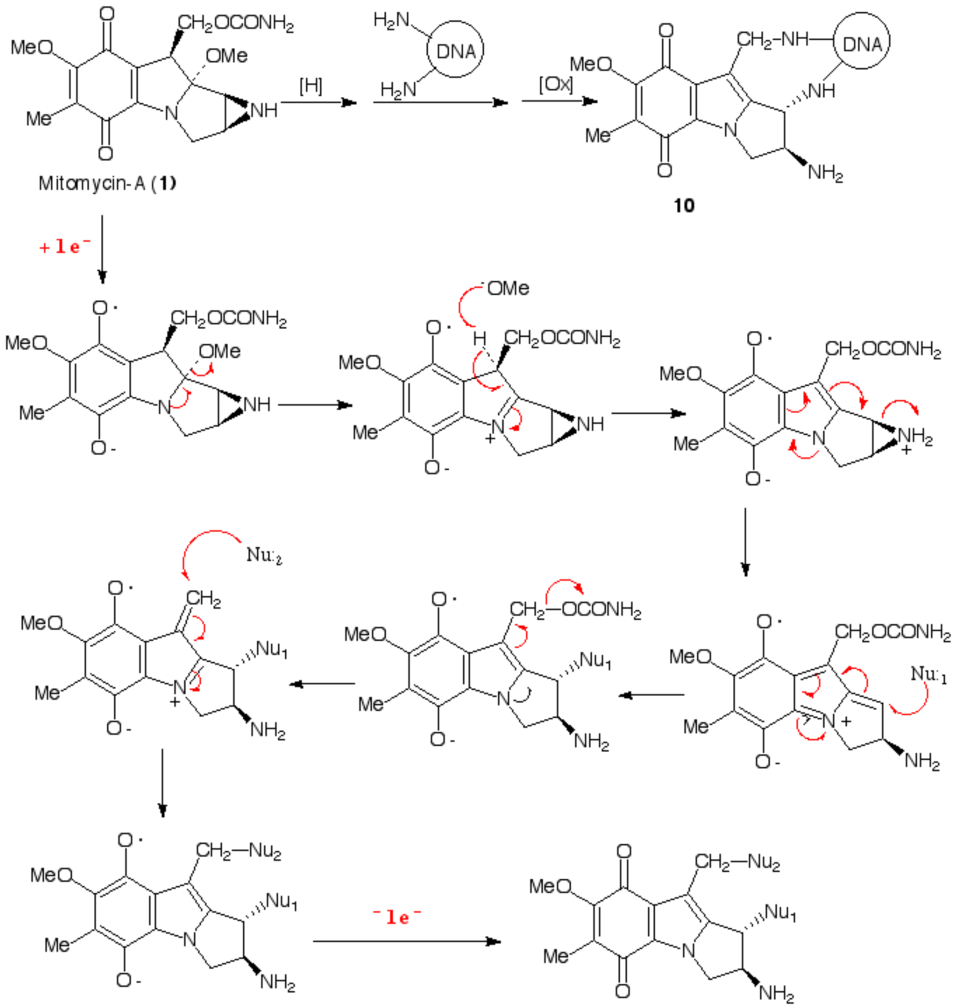
Catalysts such as $Al(OR)_3$ were also found to be quite effective

Please not that problems 226-229 are all coupled they may be retrieved by using the "**Synthesis**" plus "**Natural Product**" descriptors

## Problem 229

Contributer: **David A. Evans**
Citation: *Science* **1987**, *235*, 1204

Nakanishi, Verdine and co-workers have shown that Mitomycin-C (**1**) is a bio-alkylating agent which is known to selectively crosslink DNA, *Science* **235**, 1204 (1987). The probable mechanism by which this compound functions in this capacity has been also examined by Danishefsky, *J. Am. Chem. Soc.* **108**, 4648 (1986). He has shown that Mitomycin-C must be "primed" by reduction before it can function as an effective alkylating agent. Overall, some of the events associated with DNA crosslinking are outlined below.
Provide a detailed mechanism for the overall transformation of **1** ⇒ **10** . There is more than one sequence of events that is possible; however, you only need to show one to receive full credit.



Many of you had the alkylation steps reversed. Although this was not a serious problem with regard to partial credit, it seems reasonable to project that the aziridinium nitrogen would be a far superior leaving group (due to the relief of Ca 24 kcal/mol of ring strain) than the carbamate moiety; hence the projected order of alkylation. Others proposed that these reactions were of the $S_N2$ type. Conventional wisdom would argue against this position. For example, allylic carbamates are simply not reactive enough to react in this fashion with amines.

**Why is reduction required for bioactivation ?** Danishefsky has addressed this issue in print *J. Am. Chem. Soc.* **108**, 4648 (1986). Please read this communication which addresses this issue.

Please not that problems 226-229 are all coupled  they may be retrieved by using the "**Synthesis**" plus "**Natural Product**" descriptors

## Problem 230

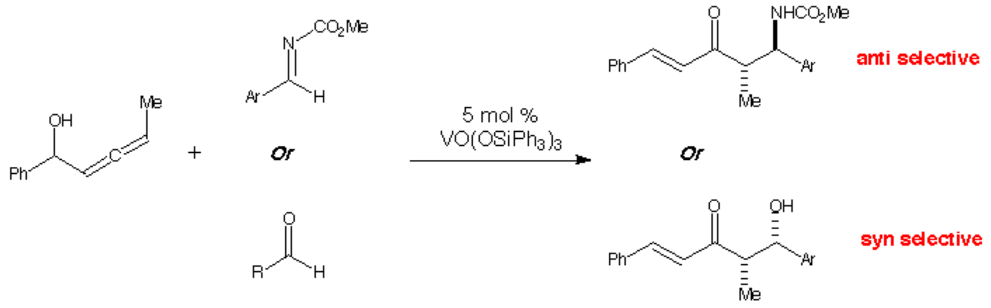
Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1986**, *110*, 6556

Consult the cited reference for an answer to this question

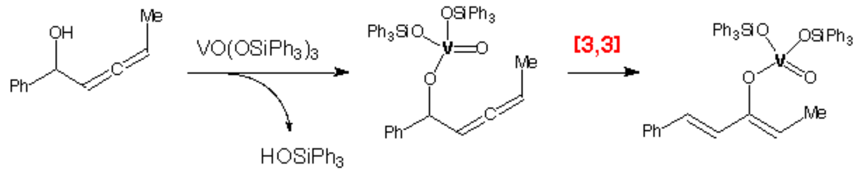
## Problem 232

Contributer: **David A. Evans**
Citation: *Angew. Chem.* **2003**, *42*, 2063

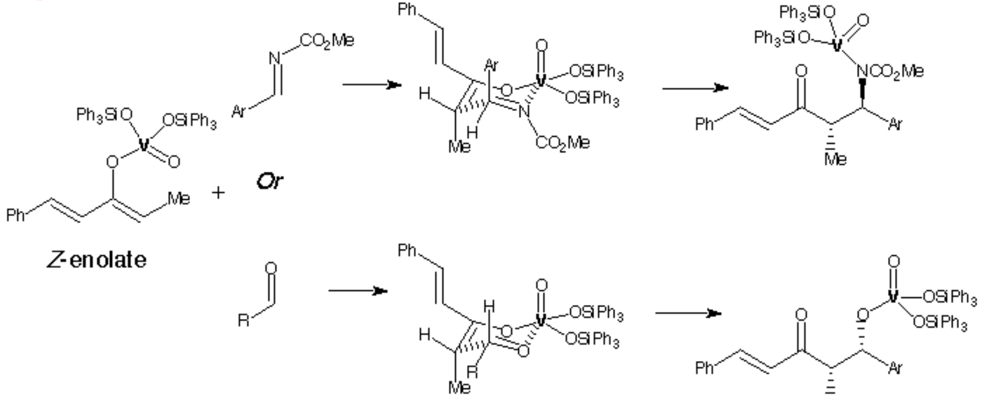
Trost *et. al.* have reported an interesting vandium catalyzed diastereoselective addition of allenols to imines and aldehydes (*Angew. Chem. Int. Ed.* **2003**, *42*, 2063). Propose a reasonable mechanism and a model accounting for the observed stereoselection. **Also see Problem 111. It is related.**



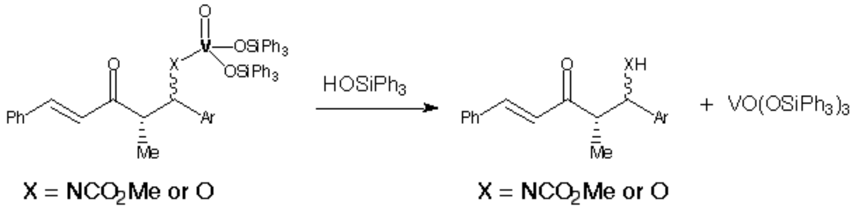
**Step-One: Olefin Isomerization**



**Step-Two Aldol Addition**

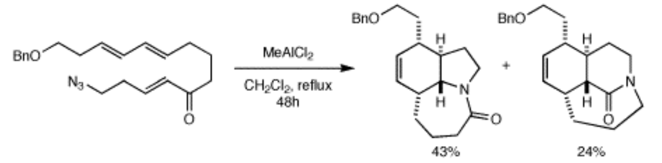


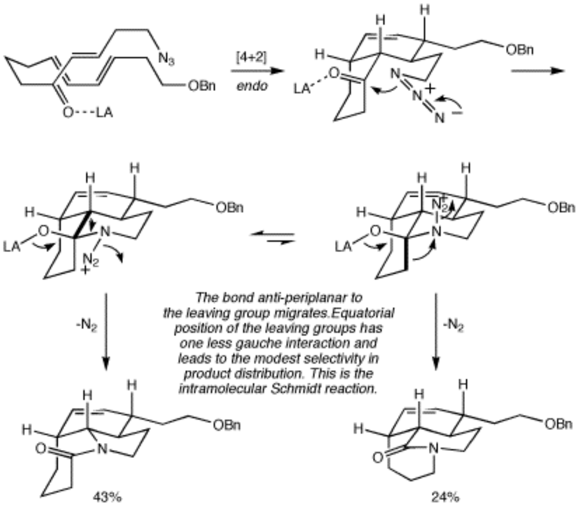
**Turnover step:**



**Problem 240** Contributer: **Carl A. Morales**
Citation: *Angew. Chem.* **2002**, *41*, 4492

In a recent report of a formal synthesis of stenine, researchers reported a tandem polycyclization which afforded the following major and minor products. Please propose a mechanism for this transformation which accounts for both products, their relative stereochemistry, and their relative distribution.



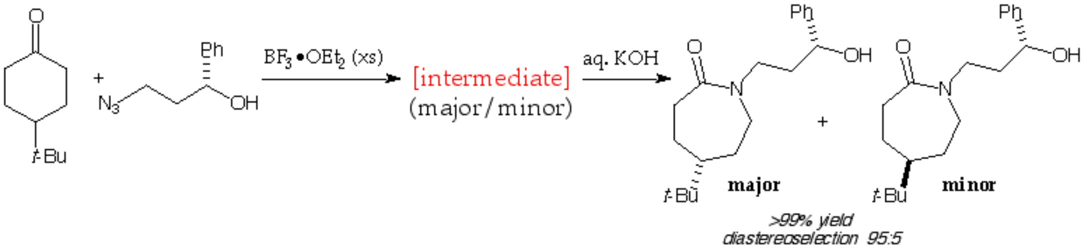


*The bond anti-periplanar to the leaving group migrates.Equatorial position of the leaving groups has one less gauche interaction and leads to the modest selectivity in product distribution. This is the intramolecular Schmidt reaction.*

Aube, J. *Ang. Chem. Int. Ed*, **2002**, *41*, 4492.

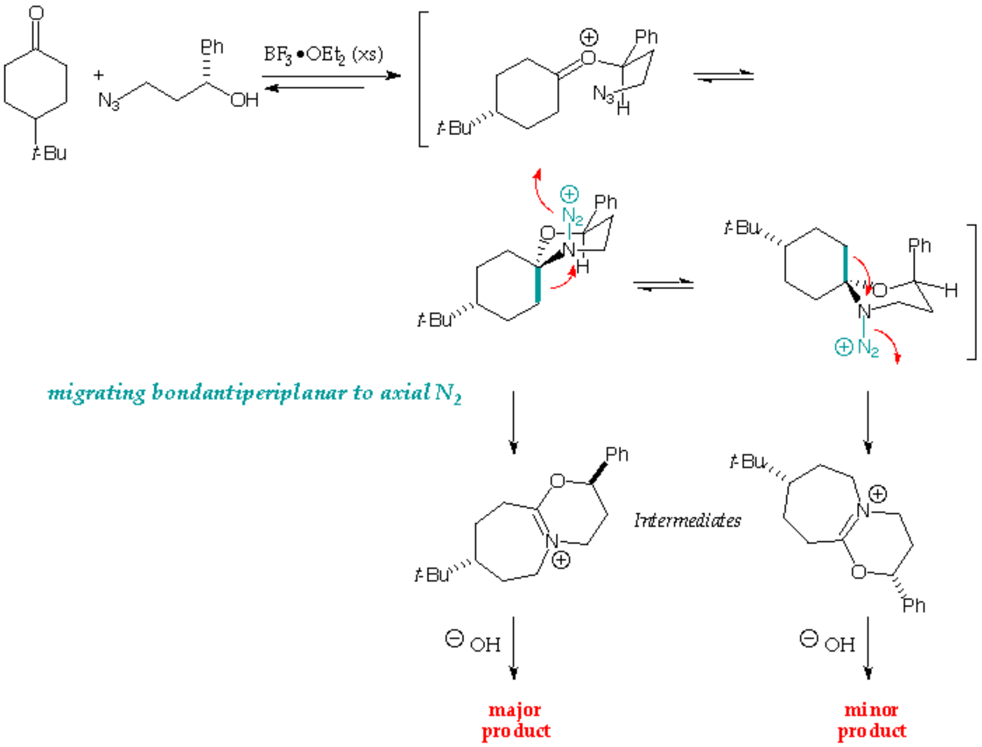
**Problem 250** Contributer: **Jake Janey**
Citation: *J. Am. Chem. Soc.* **2003**, *125*, ASAP

Aubé recently reported an asymmetric ring expansion of achiral cyclohexanones with enantiopure hydroxyalkyl azides to give enantioenriched caprolactams (*Org. Lett* **1999**, *1*, 495 and *J. Am. Chem. Soc.* **2003** ASAP). One of his reported transformations is illustrated below. The paper includes related examples with other 1,3- and 1,2-hydroxyalkyl azides and various cyclohexanones.



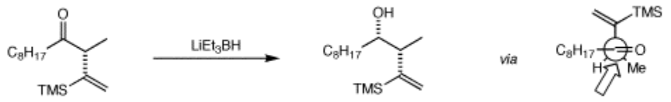
Provide a plausible mechanism for this reaction. Your answer should include three-dimensional structures that rationalize the observed stereoselection.

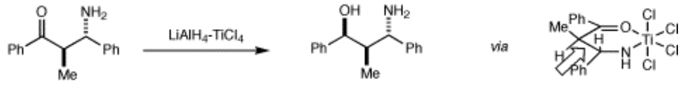
***Answer:*** **Schmidt Reaction**

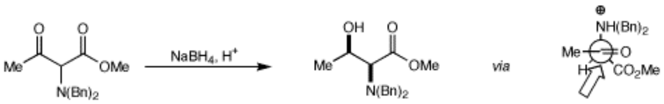


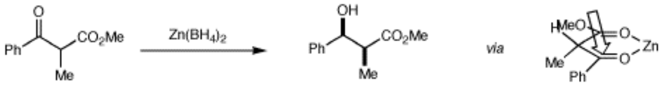
**Problem 252** Contributer: **Carl A. Morales**
Citation:

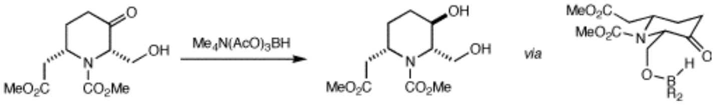
Give the major product for each of the following reactions and justify your choice. Where given a single enantiomer, predict the absolute stereochemistry. Where given racemic starting material, predict the relative stereochemistry.







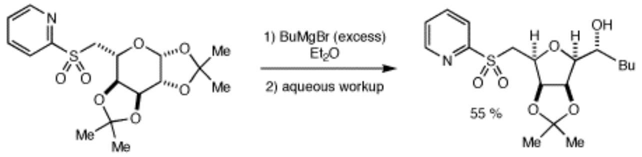


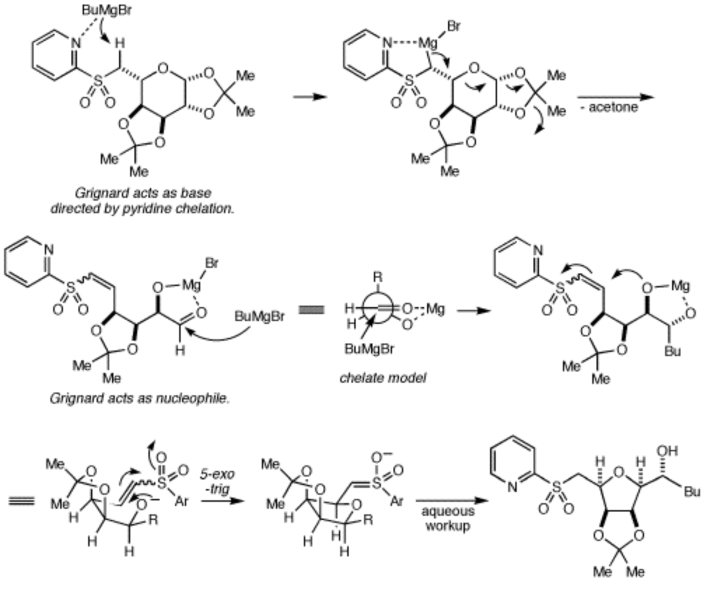


## Problem 273

Contributer: **Carl A. Morales**
Citation: *Tetrahedron Lett.* **1994**, *35*, 8377

One of the reasons that Grignard reagents can serve both as bases and nucleophiles depending on the substrates encountered. Please demonstrate your cognizance of this chemical behavior by providing a thoughtful mechanism for the transformation below taking stereochemical considerations into account.



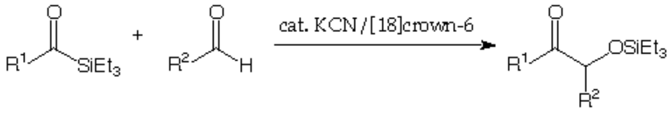


Rollin, P. *Tetrahedron Lett.* **1994**, *35*, 8377.

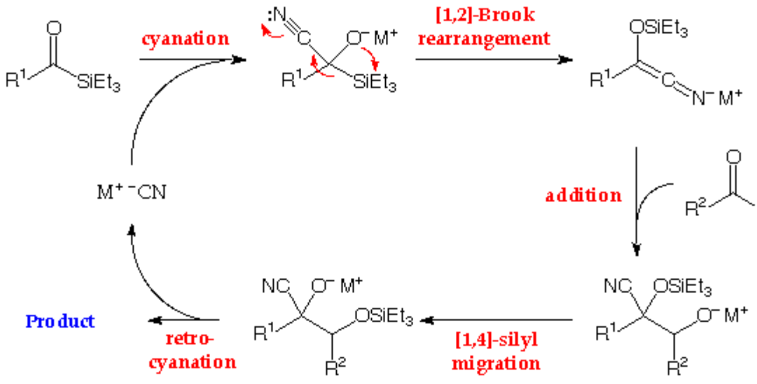
## Problem 280

Contributer: **Jake Janey**
Citation: *Angew. Chem.* **2003**, *42*, 2534-2536

J. S. Johnson has reported a way of forming α-hydroxy ketones by a cross condensation of an aldehyde and an acylsilane catalyzed by KCN/[18]crown-6 (*Angew. Chem. Int. Ed., Engl.* **2003**, *42*, 2534). This reaction is quite general for forming a variety of α-hydroxy ketones. Provide a plausible mechanism for this cyanide catalyzed reaction.



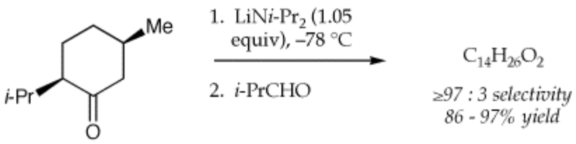
*Answer: Catalyzed cross silyl benzoin reaction*



## Problem 300

Contributer: **Keith Woerpel**
Citation: *Tetrahedron Lett.* **1997**, *38*, 9043

Isomenthone (7) has been subjected to the following reaction (J. M. Gardiner, *Tetrahedron Lett.* **1997**, *38*, 9043). Provide the product of this reaction, including the stereochemistry at all relevant stereogenic centers. Draw a transition structure that clearly indicates how this stereoisomer is formed.



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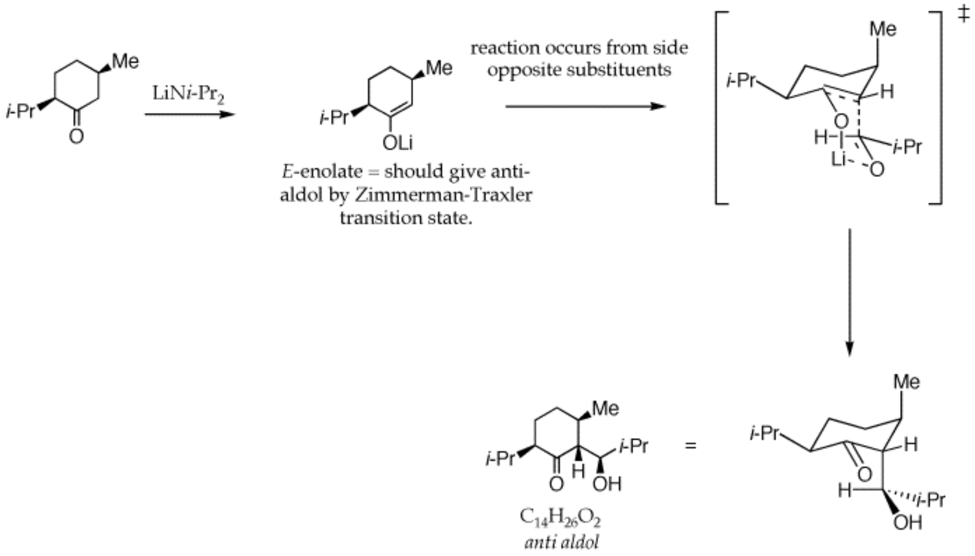
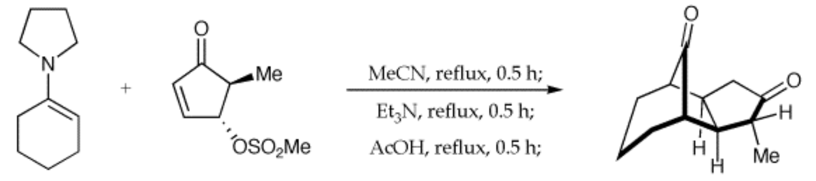

LiN*i*-Pr$_2$
reaction occurs from side opposite substituents
‡
*E*-enolate = should give anti-aldol by Zimmerman-Traxler transition state.
=
$C_{14}H_{26}O_2$
*anti aldol*

## Problem 302

Contributer: **Keith Woerpel**
Citation: *J. Am. Chem. Soc.* **1997**, *119*, 2066

West provided several examples of an one-flask annulation reaction that provides bridged bicyclic products with high diastereoeselectivity and yield (F. G. West *J. Am. Chem. Soc.* **1997**, *119*, 2066). Provide a mechanism for the following example.



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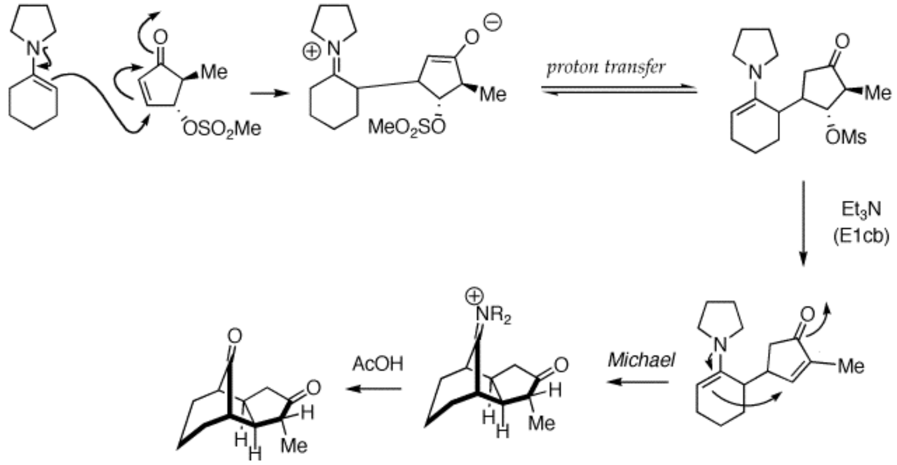
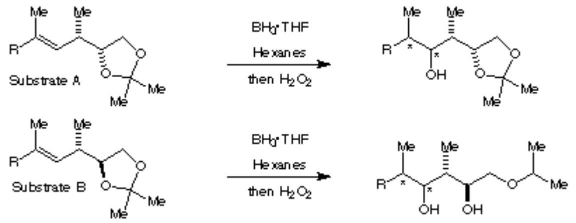


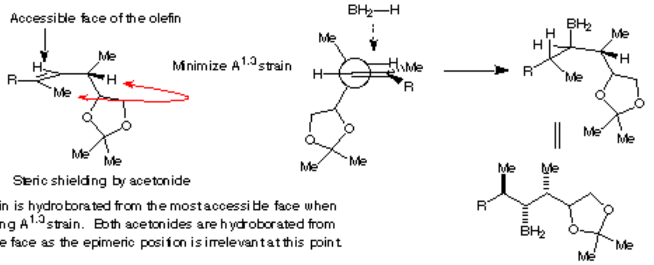
## Problem 309

Contributer: **David A. Evans**
Citation: *SynLett* **1993**, 696

The indicated olefins were subjected to hydroboration/oxidation as shown (*Synlett*, 1993, 696).

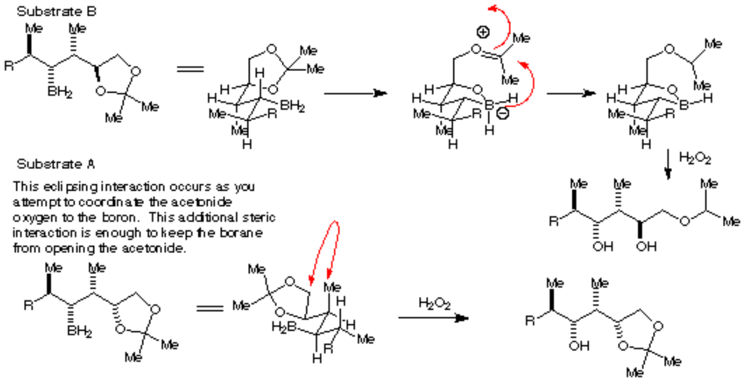


Part A. Please predict the major stereoisomer obtained from these reactions and illustrate your predictions with clear 3D drawings.


Accessible face of the olefin
Minimize $A^{1,3}$ strain
Steric shielding by acetonide
$BH_2$—H
$BH_2$

The olefin is hydroborated from the most accessible face when minimizing $A^{1,3}$ strain. Both acetonides are hydroborated from the same face as the epimeric position is irrelevant at this point.

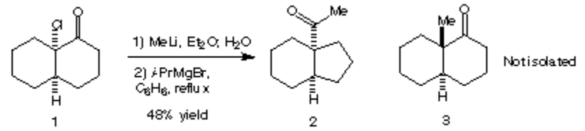
Part B. Please also explain the fact that B suffers reductive ring opening while A does not..



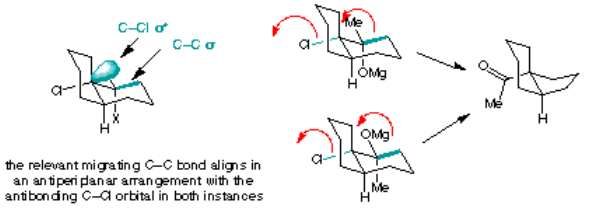
This eclipsing interaction occurs as you attempt to coordinate the acetonide oxygen to the boron. This additional steric interaction is enough to keep the borane from opening the acetonide.

**Problem 310**
Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1972**, *37*, 4090

Sisti and Citale (*J. Org. Chem.* 1972, *37*, 4090) have reported that cis chlorodecalone (1) was treated with methyllithium and a mixture of stereoisomeric alcohols was isolated. When this mixture of alcohols was converted to the derived magnesium alkoxides and heated in benzene, the ring contracted product (2) was isolated in 48% overall yield. It is interesting that none of the trans methyldecalone (3) was observed.

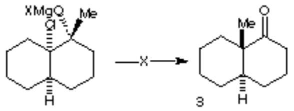


Part A. Rationalize the formation of 2 from both diastereomeric alcohols derived from 1. Please use carefully rendered three dimensional drawings to illustrate your answer.



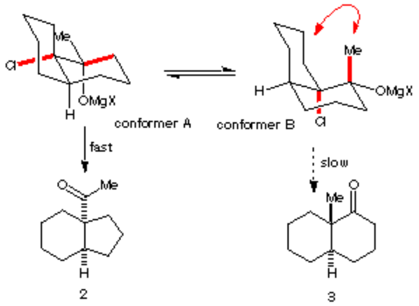
the relevant migrating C–C bond aligns in an antiperiplanar arrangement with the antibonding C–Cl orbital in both instances

Part B. Explain why the indicated alkoxide does not lead to the formation of 3.



This alkoxide, in principle, could rearrange to give either reaction product. This point is illustrated in the appended scheme.

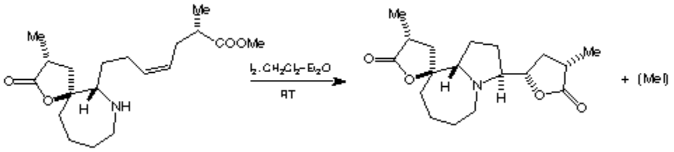
However, conformer B is strongly destabilized by the indicated double gauche pentane interaction. This destabilization is reflected in an increased activation energy for the rearrangement to 3. The rearrangement via conformer A to product 2 does not suffer such destabilization.



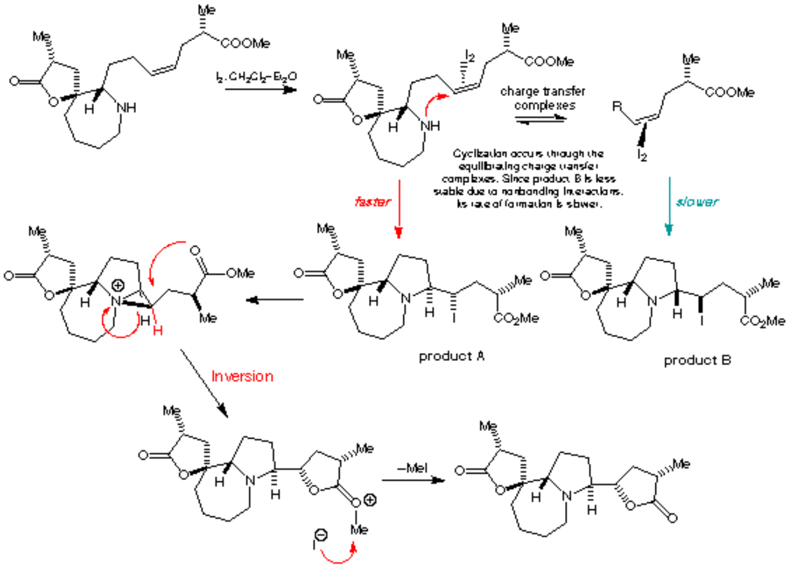
## **Problem 311**

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1986**, *111*, 1923

The iodine-induced transformation shown below is a key step in the Williams synthesis of croomine (*JACS* 1989, *111*, 1923). Given the stereochemical outcome of the illustrated transformation, propose a detailed mechanism for this reaction sequence. Williams has recently provided another closely reaction of the same design (*Org. Lett* 2003, *5*, 3361).



Answer

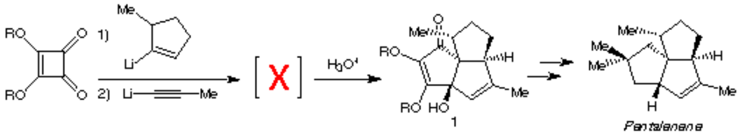


Cyclization occurs through the equilibrating charge transfer complexes. Since product B is less stable due to nonbonding interactions, its rate of formation is slower.

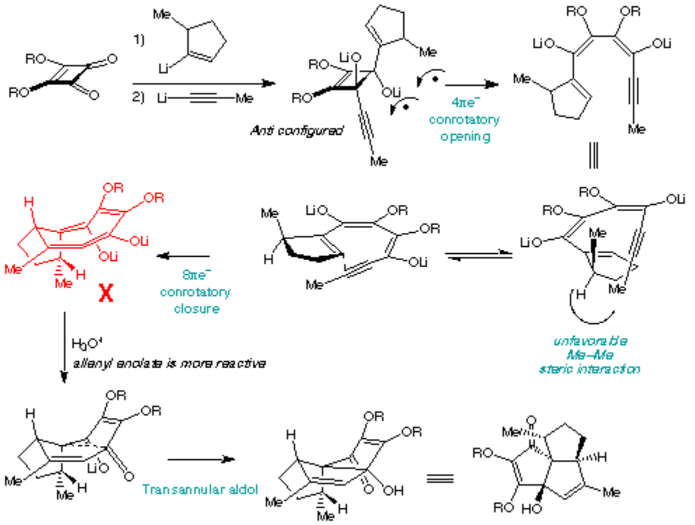
## Problem 328

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2002**, *4*, 4547-4549

A synthesis of the hydrocarbon pentalenene was recently disclosed by Paquette and co-workers (*Org. Lett.* 2002, *4*, 4547-4549). The pivotal reaction cascade that affords the pentalenene core 1 is illustrated below.



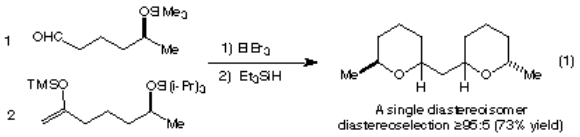
Please provide a mechanism for the reaction cascade that results in the production of the tricyclic core 1. Your answer should include clear 3-D drawings where relevant and should clearly identify intermediate X.



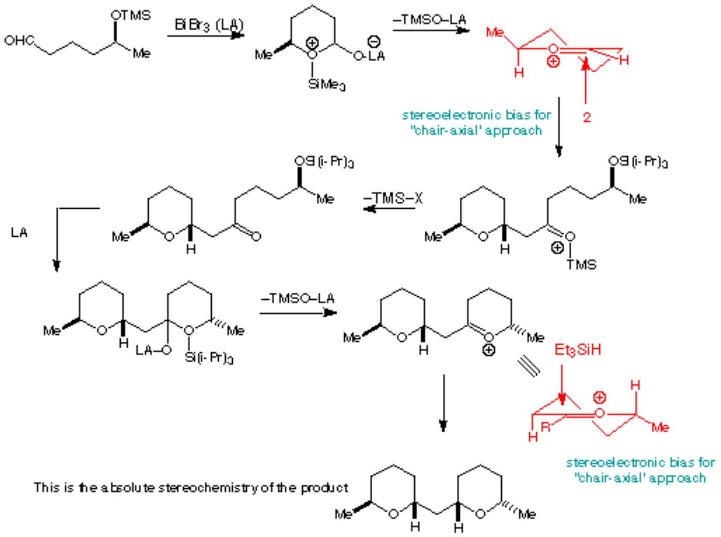
## Problem 329

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2003**, *125*, 11456-11457

P. A. Evans and co-workers have recently reported a highly diastereoselective approach to the construction of linked tetrahydropyrans (*JACS* 2003, *125*, 11456-11457). One of their cases is illustrated in Eq 1. In this transformation BiBr$_3$ is employed as a mild Lewis acid.



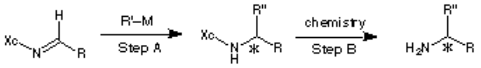
Please provide a mechanism for the reaction cascade that results in the production of the illustrated product. Your answer should include clear 3-D drawings where relevant and should provide the stereochemistry of the major product diastereoisomer.


OHC
OTMS
Me
BiBr$_3$ (LA)
Me
O
SiMe$_3$
O-LA
–TMSO–LA
Me
H
O
H
2
stereoelectronic bias for "chair-axial" approach
OSi(i-Pr)$_3$
Me
Me
O
H
O
TMS
–TMS–X
LA
Me
O
H
LA–O
O
Si(i-Pr)$_3$
Me
–TMSO–LA
Me
O
H
O
Me
Et$_3$SiH
H
R
O
H
Me
stereoelectronic bias for "chair-axial" approach
This is the absolute stereochemistry of the product
Me
O
H
H
O
Me

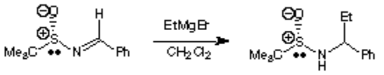
## Problem 330

Contributer: **David A. Evans**
Citation: *Tetrahedron* **1999**, *55*, 8883

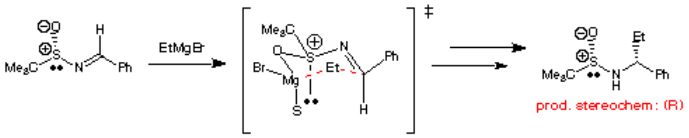
Chiral auxiliaries (Xc) are routinely employed to control the absolute stereochemistry of the addition or organometallic reagents to imines (Step A). A design requirement of these controllers is that they may be readily cleaved after the addition step (Step B). In the two parts of this question posed below are presented two well-established chiral controllers that employ chelate organization as an integral part of lthe chirality transfer process.



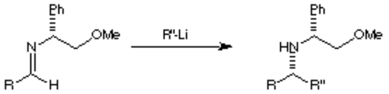
Part A. Provide a mechanism for the following transformation reported by Ellman and co-workers. (*Tet*, 1999, 8883). Include a clear transition state representation that predicts the the major product diastereomer. Clearly illustrate the the absolute stereochemistry of the product.



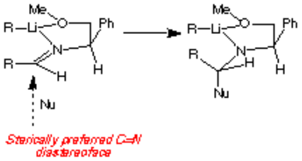
diastereomer ratio 92:8



Part B. The following stereoselective transformation has been reported by Fujisawa (*Chem.Lett.* 1991, 1555). Given the sterostructure of the product, rationalize the stereochemical outcome.



diastereomer ratio >97:3

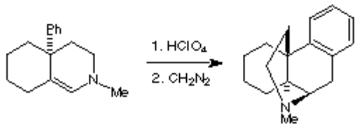


The stereochemical outcome of this reaction has been rationalized by Fujisawa through the chelate-organized imine complex shown on the left. In this study diastereoface selectivity was noted to be strongly dependant on the nature of the organometallic reagent.

## Problem 333

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1980**, *102*, 5955-5956

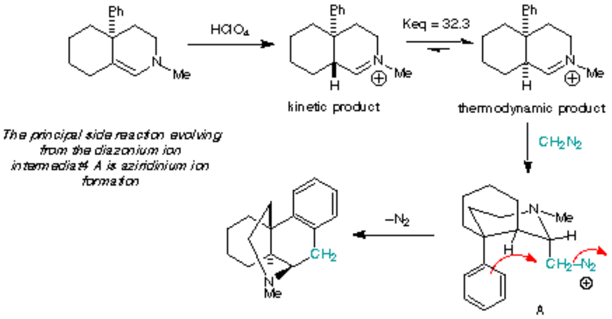
Evans and Mitch have reported reported the short approach to the synthesis of the morphine skeleton (*JACS* 1980, *102*, 5956).



30% yield

Morphine alkaloid skeleton

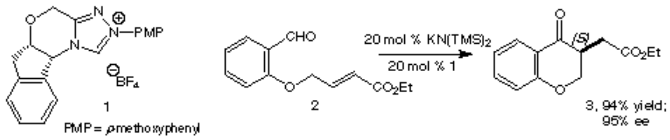
Provide a mechanism for this interesting transformation.



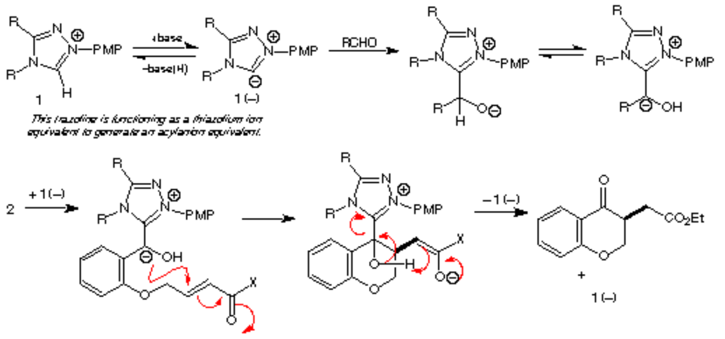
## Problem 334

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2002**, *124*, 10298

The development of chiral variants of the Stetter reaction is a current objective in the chemical literature. Such a study has been recently reported by Rovis and Co-workers (*JACS* 2002, *124*, 10298). In the presence of 20 mol percent of triazolium salt 1, and an equal amount of KN(TMS)$_2$, 2 is transformed into 3 in 94% yield and 95% ee.



Provide a mechanism for this rearrangement in the space below. You do not need to account for the absolute stereochemical outcome of this reaction in your answer.

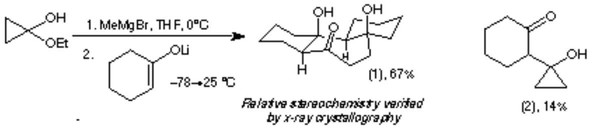


*This triazoline is functioning as a triazolium ion equivalent to generate an acylanion equivalent.*

## Problem 337

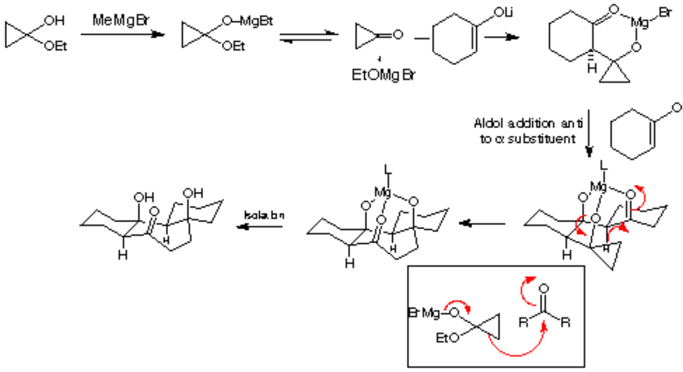
Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1986**, *108*, 8313

Helquist has reported the interesting enolate-based ring-forming process illustrated below (*JACS* 1986, *108*, 8313). In this experiment, the MeMgBr was added to the cyclopropanone hemiketal. The cyclohexanone enolate (2 equiv) was then cannulated into the reaction vessel. In addition to the indicated product 1, ~14% of the cyclopropanone aldol adduct 2 was obtained. If 2 is treated under the stated reaction conditions, an 80% of 1 is obtained. The selection of Mg(II) to mediate the stereochemical outcome of this reaction is important.



*Relative stereochemistry verified by x-ray crystallography*

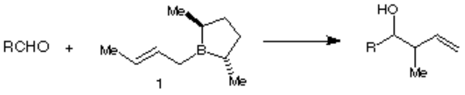
Please provide a plausible mechanism for this transformation. Use 3-dimensional representations where appropriate to illustrate your answer.

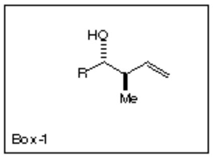


## Problem 339

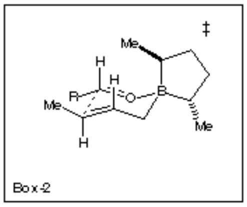
Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **1987**, *52*, 4831

The $C_2$-symmetric allylborane 1 introduced by Masamune (*J. Org. Chem.* 1987, *52*, 4831) has had an important impact on the design of chiral aldol and allylation catalysts.





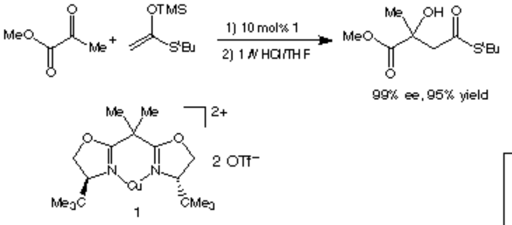
Provide the absolute stereochemistry of the product of this reaction in Box-1.
Provide a 3-dimensional drawing of the transition state for this reaction in Box-2.

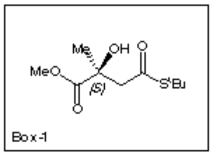


## Problem 340

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **1999**, *121*, 686

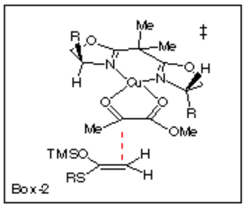
The $C_2$-symmetric cationic Cu(II) complex 1 is a chiral Lewis acid catalyst that exhibits good chelating potential. The utilization of 1 in the catalyzed Mukaiyama aldol addition is illustrated below (*JACS* 1999, *121*, 686).





Provide the absolute stereochemistry of the product of this reaction in Box-1.
Provide a 3-dimensional drawing of the transition state for this reaction in Box-2.

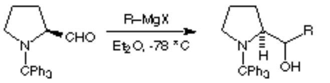
*Hint: Cu(II) complexes strongly prefer square-planar geometries*



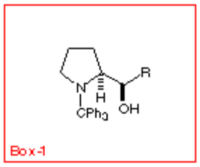
## Problem 341

Contributer: **David A. Evans**
Citation: *J. Org. Chem.* **2003**, *68*, 9747

The illustrated stereoselective Grignard additions to trityl-protected prolinal have recently been reported (*JOC*, 2003, *68*, 9747). These additions proceed with exceptional stereochemical control. A clue as to the operational mechanism for stereocontrol follows from the observation that the allylation product produced by Grignard addition has the same stereochemistry as the allylation product produced by the addition of allylsilane/$BF_3 \cdot OEt_2$.

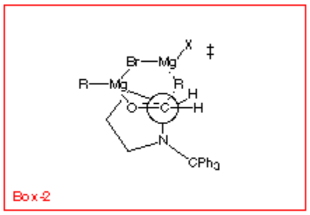


*diastereoselection ≥98:2*



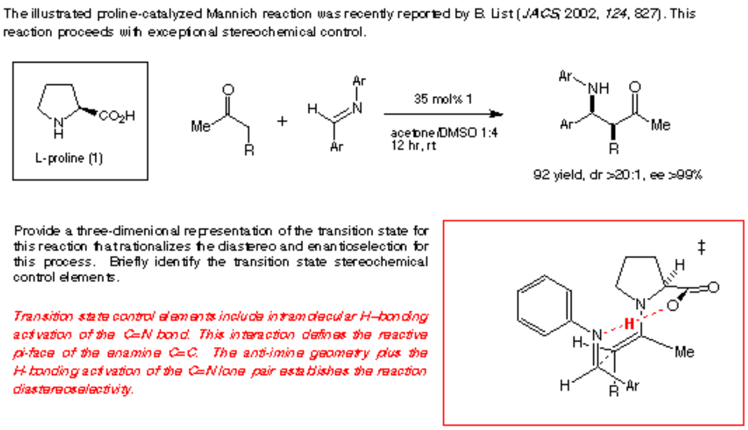
Please draw the absolute stereochemistry of the product in Box-1. In Box-2 provide a three-dimenional representation of the transition state for this reaction that rationalizes the diastereoselection for this process. Briefly identify the transition state stereochemical control element(s) below.

*Since these additions could operate by either a chelate-controlled or a Felkin-controlled process, the provided clue substantiates that Felkin control is operational and that the trityl-protected nitrogen does not participate in chelate organization. This is actually one of the points brough out in the paper. the transition structure should: A) adhere to the Felkin Model; B) should exhibit the bimetallic addition motif.*



## Problem 342

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2002**, *124*, 827



The illustrated proline-catalyzed Mannich reaction was recently reported by B. List (*JACS* 2002, *124*, 827). This reaction proceeds with exceptional stereochemical control.

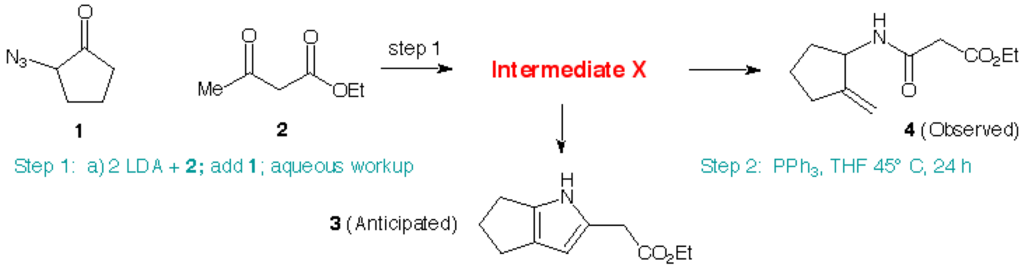
Provide a three-dimenional representation of the transition state for this reaction that rationalizes the diastereo and enantioselection for this process. Briefly identify the transition state stereochemical control elements.

*Transition state control elements include intramolecular H–bonding activation of the C=N bond. This interaction defines the reactive pi-face of the enamine C=C. The anti-imine geometry plus the H-bonding activation of the C=N lone pair establishes the reaction diastereoselectivity.*

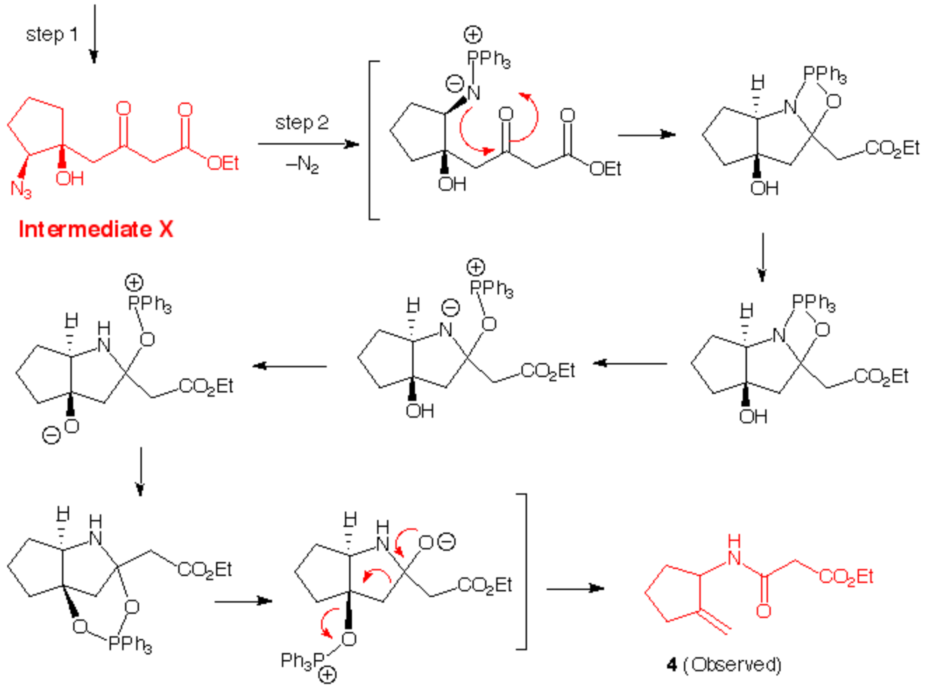
## Problem 343

Contributer: **David A. Evans**
Citation: *Chem. Commun.* **2003**, 3044

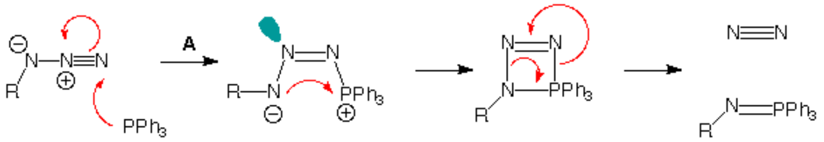
Langer and co-workers recently reported the interesting *errant* Staudinger reaction illustrated below ( *Chem Comm.* **2003**, 3044). The anticipated reaction product was pyrrole **3** while the observed product was **4**.


1
2
step 1
Intermediate X
4 (Observed)
Step 1: a) 2 LDA + 2; add 1; aqueous workup
Step 2: PPh3, THF 45° C, 24 h
3 (Anticipated)

Provide a detailed mechanism for this transformation.



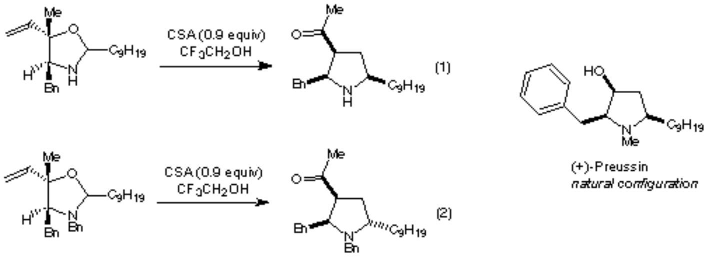
**Mechanism of the Staudinger Reaction**



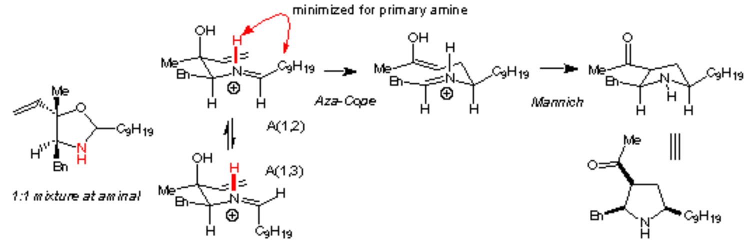
In Step A, nucleophiles perferentially add to azides to give an intermediate having the cis geometry as shown as documented by Trost (*JACS* **1983**, *105*, 1054) for Grignard reagents. A stereoelectronic argument may be used to account for the cis stereoselection.

**Problem 359** Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.*

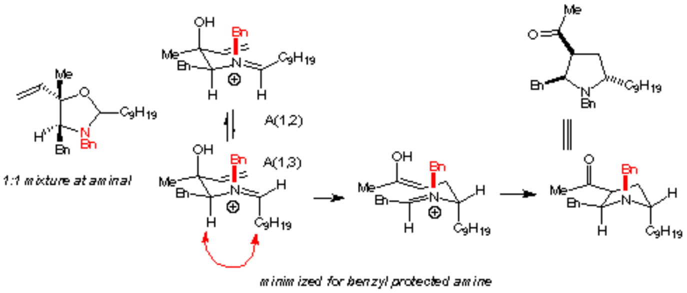
An elegant enantiodivergent synthesis of the potent anti-fungal reagent Preussin was reported by Overman (*JACS* 1994, 11241.).



Part A. Provide a mechanism for the transformation illustrated in Eq 1. Where stereochemicasl issues are involved, 3-dimensional drawings should be employed.



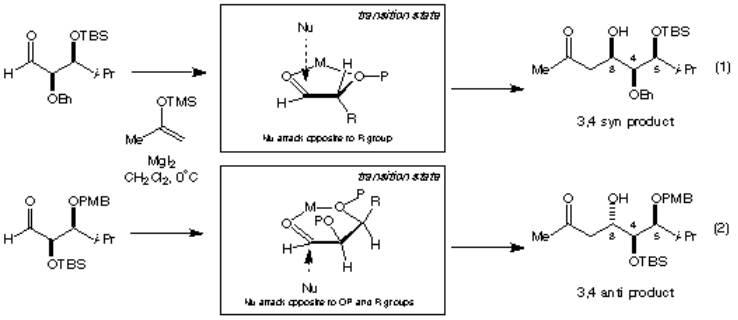
Part B. Provide a mechanism for the transformation illustrated in Eq 2. Where stereochemicasl issues are involved, 3-dimensional drawings should be employed.



## Problem 362

Contributer: **David A. Evans**
Citation: **2003**

The two illustrated $MgI_2$–promoted Mukaiyama aldol reactions occur with high diastereoselectivity (Eq 1, 2). In contrast, only poor selectivity is observed in both reactions when $MgI_2$ is replaced with $BF_3 \cdot OEt_2$. Provide a transition state model that explains the formation of the 3,4 syn product in (Eq 1) and the 3,4 anti product in (Eq 2). Assume that the Bn and PMB protecting groups are chemically equivalent. (Victor Cee, Ph.D. Thesis, pgs. 82-87).

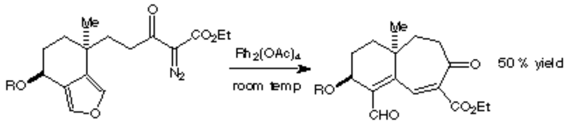


When the chelating protecting group is in the alpha position (Eq1), a five member chelate is formed and incoming nucleophile attacks from pi face opposite to the R group (TS-1). In contrast, a six-membered chelate is formed when the chelating protecting group is in the beta position and the nucleophile approaches from the face away from both the OP and R groups. The observation that $BF_3 \cdot OEt_2$ gives poor selectivity implies that the reaction is not simply under Felkin control, as one may predict for Eq 2.

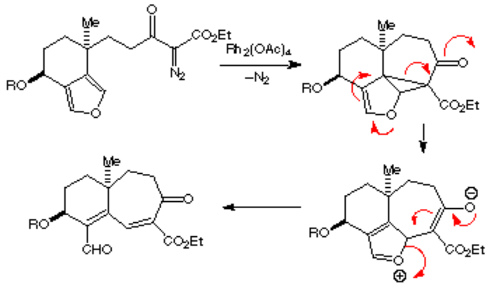
## Problem 368

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2003**, *5*, 4113

The following transformation was recently reported by Trauner and co-workers (*Organic Lett.* 2003, *5*, 4113) as a pivotal reaction in the synthesis of specific members of the guanacastepene diterpenes. These natural products have attracted interest as potent antiobiotics against *Staphylococcus aureus*.



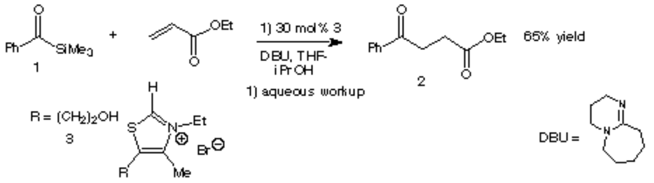
Provide a mechanism for the transformation illustrated above.

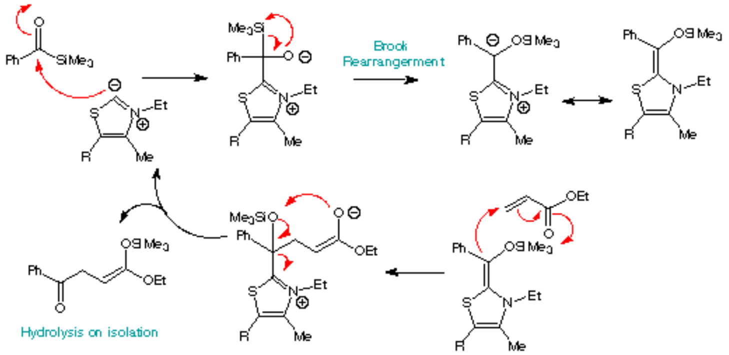


## Problem 369

Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2004**, *ASAP*,

The first example of a "Silyl-Stetter reaction" will appear in the literature shortly (Scheidt, *JACS* 2004, 125, in press). Provide a mechanism for this transformation.

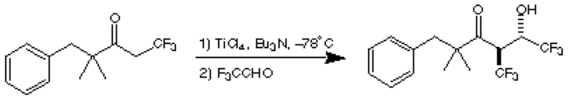




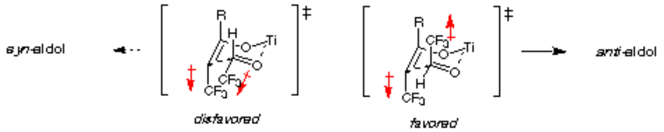
## Problem 379

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2003**, *5*, 4807

Mikami and co-workers have recently reported the illustrated aldol reaction (*Organic Lett.* 2003, *5*, 4807). This result was unexpected in light of the fact that the intervening (Z) enolate geometry was unequivocally established. The authors conclude that "dipole effects" are responsible for the observed stereochemical outcome. Please reproduce the authors' rationale for the observed reaction diastereoselection.



83% yield, 81% de

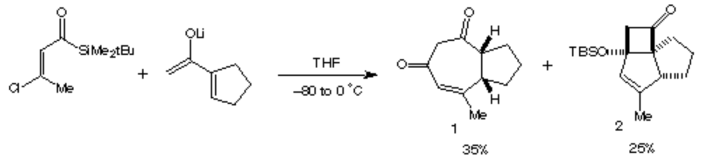


*the strongly polarizing $CF_3$ groups create strong dipoles, and the minimization of these dipoles (most favorable with diaxial $CF_3$ groups) overrides the steric bias for the syn-aldol transition state*

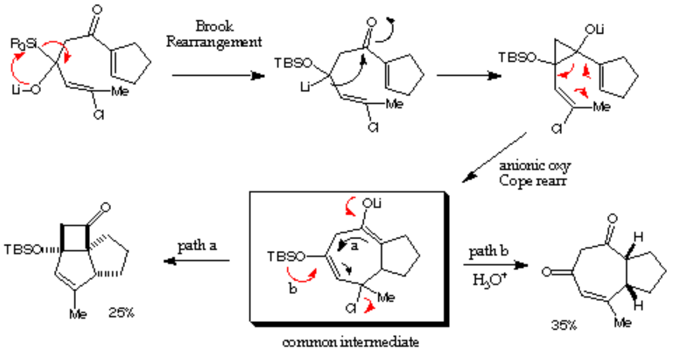
## Problem 380

Contributer: **David A. Evans**
Citation: *Organic Lett.* **1999**, 677

Takeda and co-workers have developed an efficient strategy for the synthesis of fused 5,7 ring systems by reacting acylsilanes with lithium enolates (*Org. Lett.* 1999, 677). Although the 5,7 bicyclic product 1 is often observed, the nature of the enolate nucleophile can affect the course of the reaction.



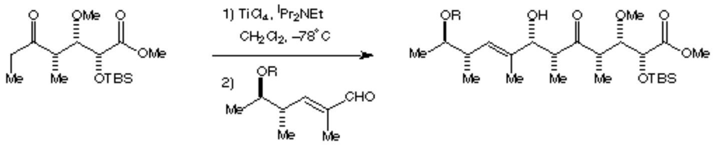
Provide a mechanism for the formation of both the anticipated 5,7 bicycle 1 and the tricyclic ketone 2.

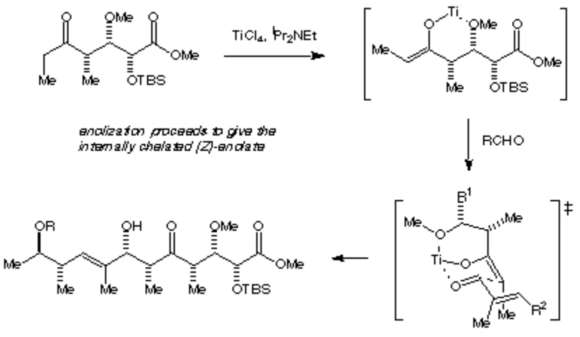


## Problem 381

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2002**, *4*, 4739

In 2002 Roush reported the stereoselective synthesis of the C1–C12 fragment of Tedanolide (*Organic Lett.* 2002, *4*, 4739). The illustrated aldol reaction was employed. Provide a clear 3-D transition state which rationalizes the stereoselectivity of this reaction.



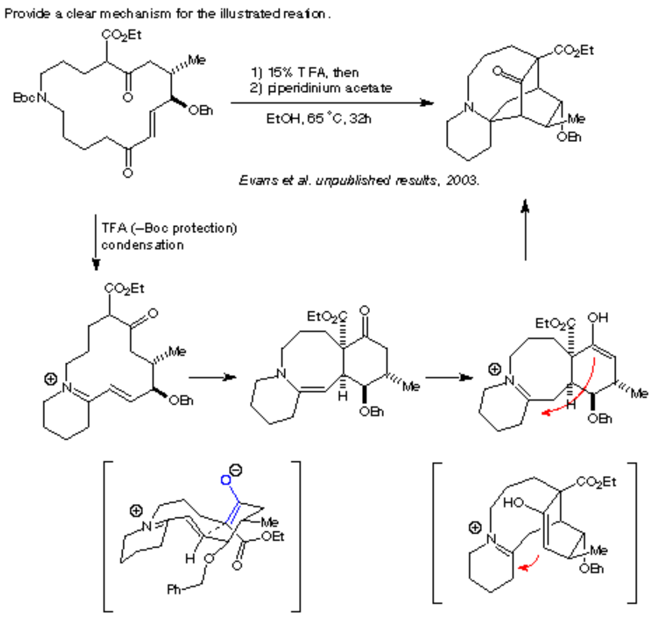


*enolization proceeds to give the internally chelated (Z)-enolate*

*chelation controls facial addition to the enolate through a closed transition state to give the syn-aldol*

## Problem 382

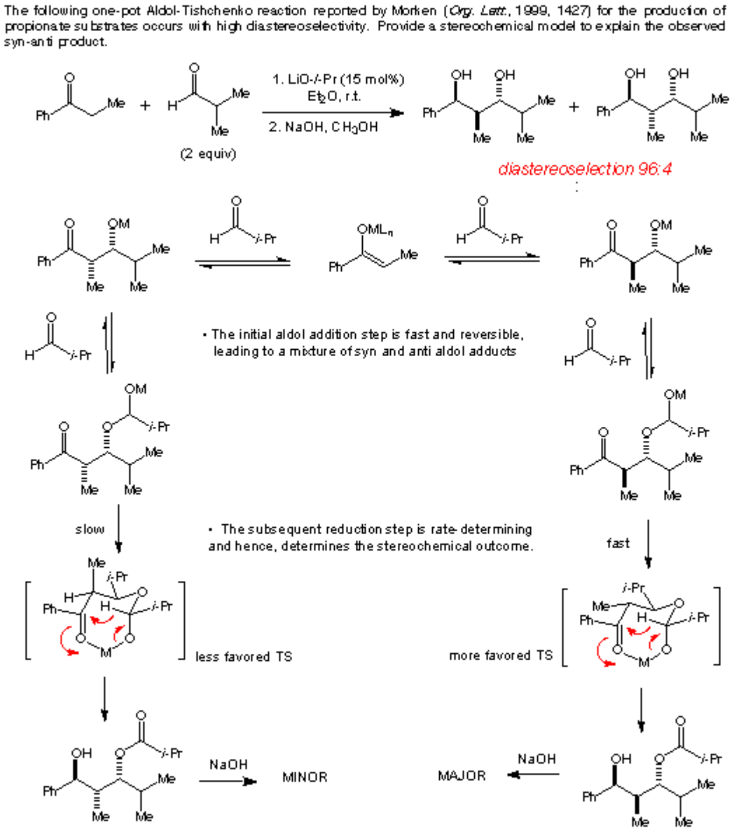
Contributer: **Jonathan Scheerer**
Citation: *Angew. Chem.* **2005**, *44*, 6038-6042


Provide a clear mechanism for the illustrated reaction.

Evans et al. unpublished results, 2003.

## Problem 385

Contributer: **David A. Evans**
Citation: *Organic Lett.* **1999**, *1*, 1427

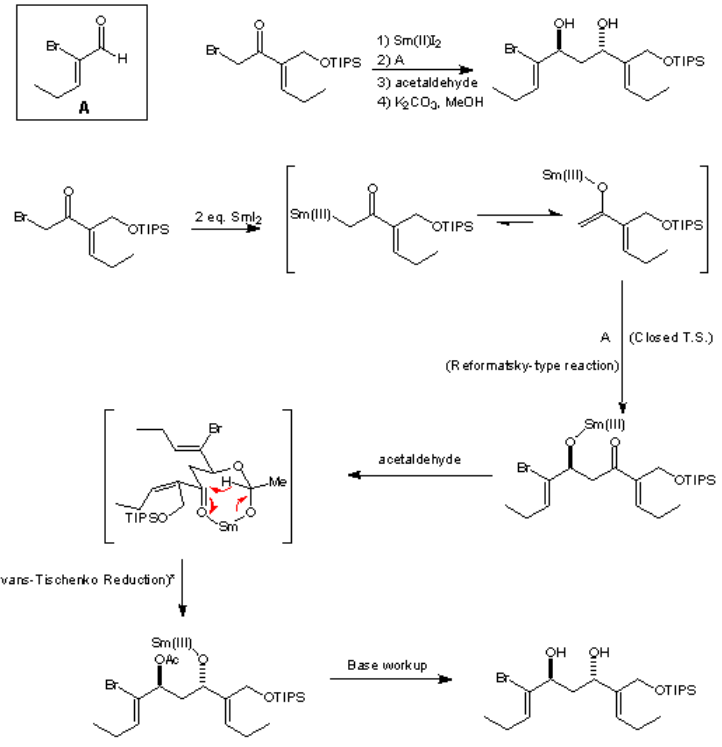

The following one-pot Aldol-Tishchenko reaction reported by Morken (*Org. Lett.*, 1999, 1427) for the production of propionate substrates occurs with high diastereoselectivity. Provide a stereochemical model to explain the observed syn-anti product.

- The initial aldol addition step is fast and reversible, leading to a mixture of syn and anti aldol adducts
- The subsequent reduction step is rate-determining and hence, determines the stereochemical outcome.

## Problem 386

Contributer: **David A. Evans**
Citation: *Organic Lett.* **2002**, *4*, 3087

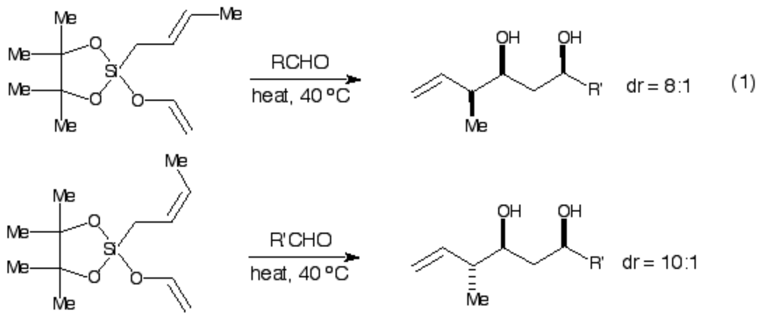
A recent paper by Wood and co--workers presented the one-pot transformation shown below (*Org. Lett.* 2002, *4*, 3087). In the space provided, please propose a mechanism that explains the relative stereochemistry of the product diol.



*"Samarium-Catalyzed Intramolecular Tishchenko Reduction of β-Hydroxy Ketones. A Stereoselective Approach to the Synthesis of Differentiated Anti 1,3-Diol Monoesters". Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* 1990, *112*, 6447-6449.

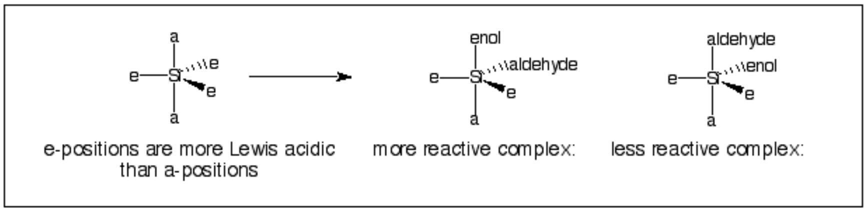
**Problem 392** Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2002**, *124*, 10672

The following transformation was recently reported by Leighton (*J. Am. Chem. Soc* **2002**, *124*, 10672).

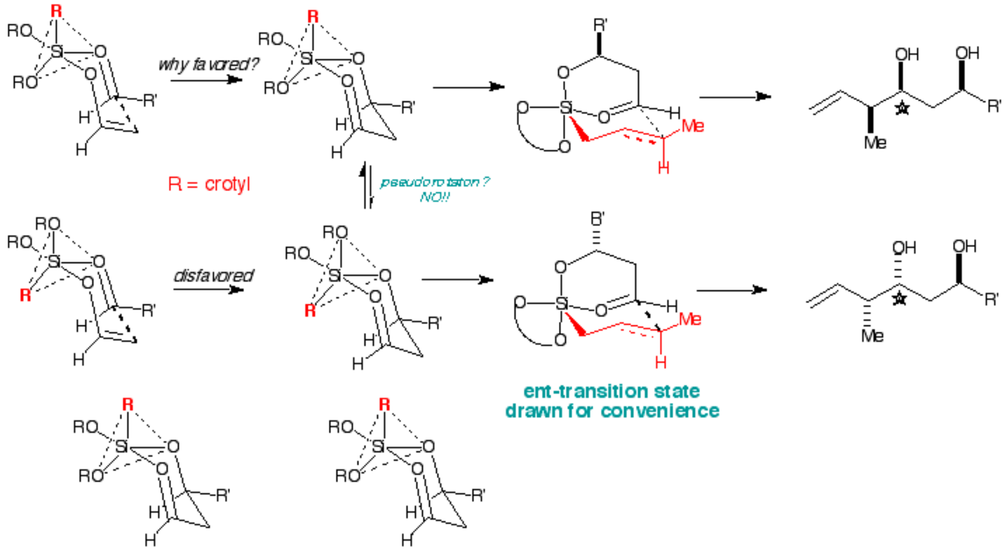


Provide a plausible mechanism for this transformation in the space below:

**Step I:** Make decision on most reactive geometry of pentacoordinate silicon.

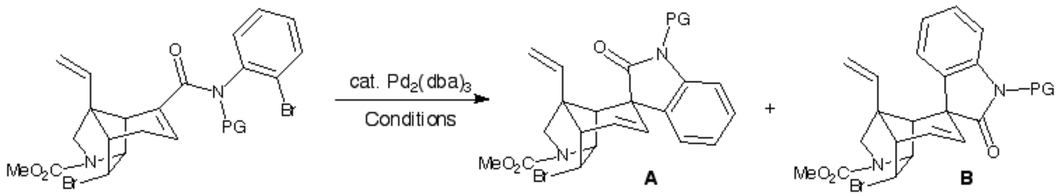


**Step II:** Make decision on which geometry is preferred. C=O face selectivity at (N) is defined in the *first* addition.



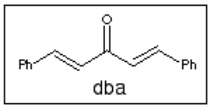
**Problem 395** Contributer: **Andre Beauchemin**
Citation: *Tetrahedron Lett.* **1992**, *33*, 4859

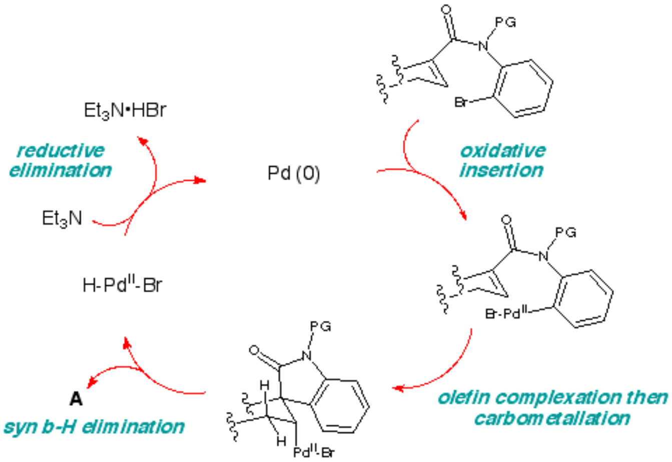
The Heck reaction is a powerful method to form C-C bonds and an efficient approach to the formation of quaternary carbon centers . A specific example is shown below (Madin and Overman, *TL* **1992**, *33*, 4859).



| Conditions | **A : B** |
|---|---|
| $Et_3N$ (10 equiv), toluene, 110 °C | 89:11 |
| $Ag_3PO_4$ (2 equiv), THF, 66 °C | 3:97 |

**1. Postulate a catalytic cycle for this reaction.**

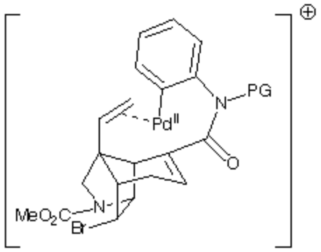




Catalytic cycle shown for $Et_3N$ conditions

For a general discussion see: Nicolaou and Sorensen *in Classics in Total Synthesis* (VCH), Chapter 31

**2. Provide a rationale for the divergent stereochemical outcome.**

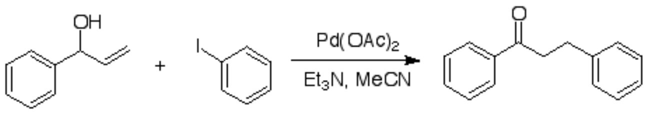


- $Ag_3PO_4$ leads to formation of cationic palladium intermediate (+AgBr)
- Axial vinyl substituent acts as directing group

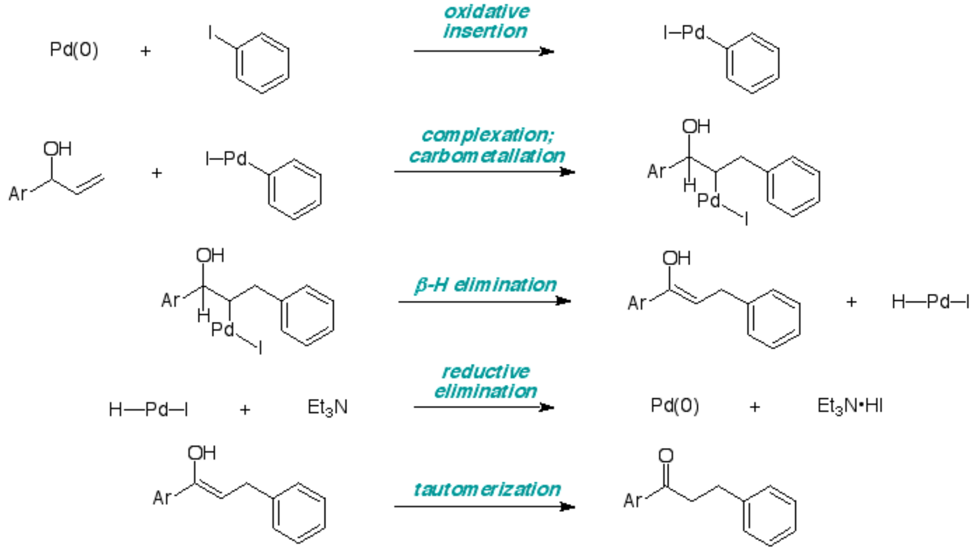
## Problem 398

Contributer: **Andre Beauchemin**
Citation: *Tetrahedron* **2001**, *57*, 7449

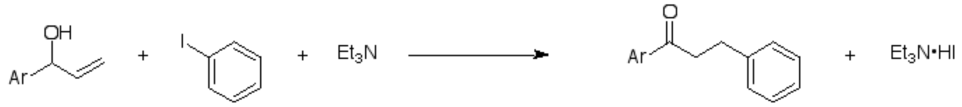
The Heck reaction is one of the most powerful transition metal C–C bond forming reactions (Whitcombe, et al, *Tetrahedron* **2001**, *57*, 7449). A typical example of this transformation is shown below.



Provide a plausible mechanism for this transformation and illustrate the individual steps in the catalytic cycle with a series of balanced equations. *Note: $Pd(OAc)_2$ is reduced to form Pd(0) under the reaction conditions. Do not concern yourself with this reduction step.*



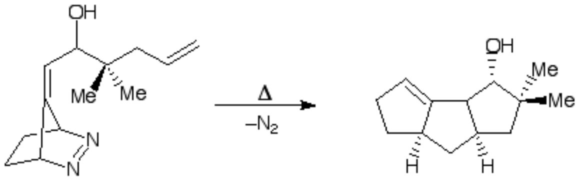
**Summation:**



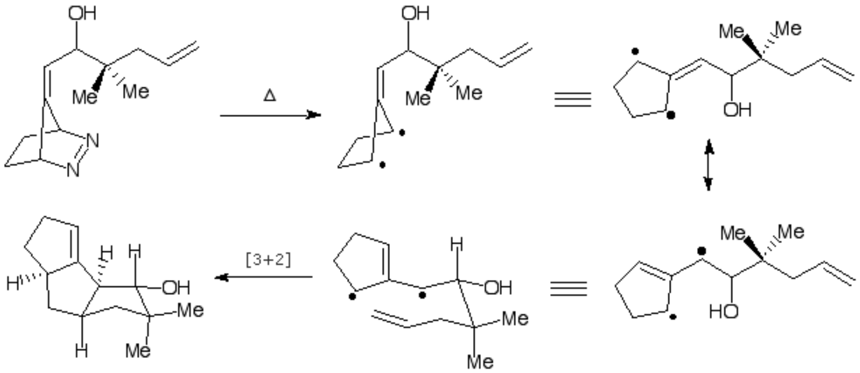
## Problem 402

Contributer: **Phillip S. Baran**
Citation: *Chem. Rev.* **1986**, *86*, 875

Little and co-workers employed this stunning transformation in a series of studies directed toward the synthesis of diketocoriolin B. (For a relevant review see *Chem. Rev.* **1986**, *86*, 875).



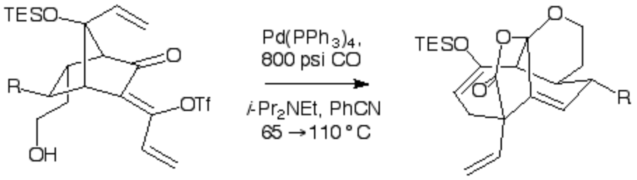
Please provide a mechanism for this transformation, accounting for stereochemistry when necessary.



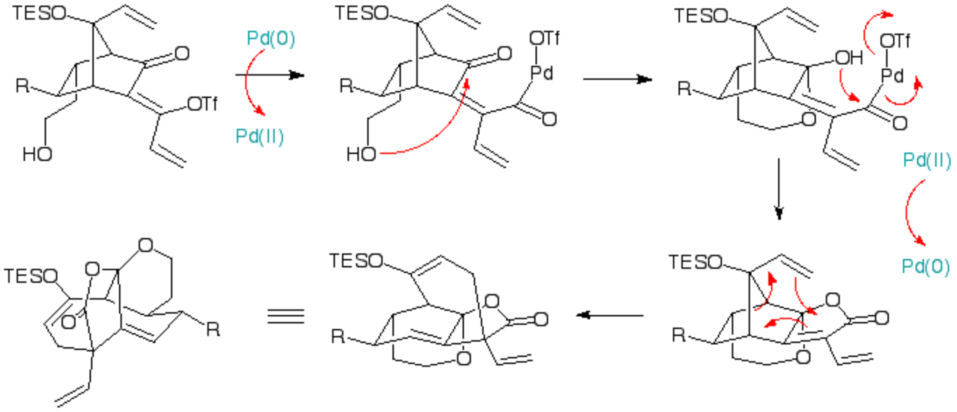
## Problem 404

Contributer: **Phillip S. Baran**
Citation: *Organic Lett.* **2000**, *2*, 2905

Leighton and Bio have recently disclosed the following approach to the core of CP-263,114 ( *Org. Lett* **2000**, 2905).

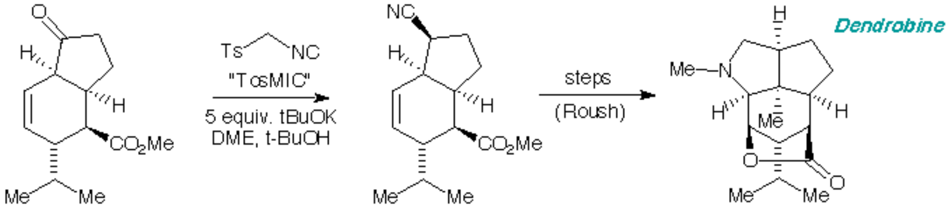


Please provide a mechanism for this transformation.

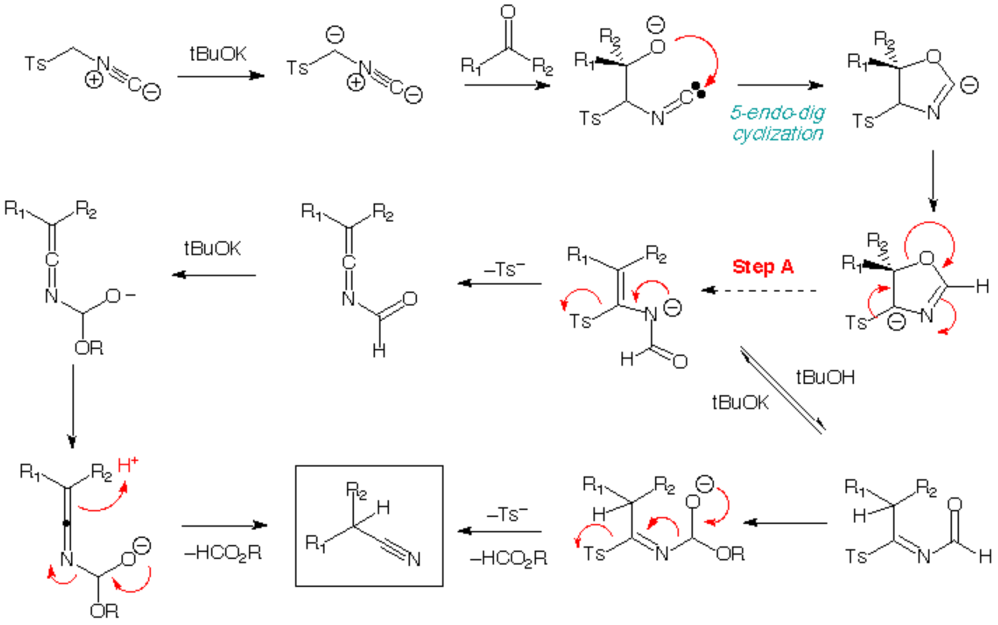


**Problem 409** Contributer: **Dan O,Malley**
Citation: *J. Org. Chem.* **1977**, *42*, 3114

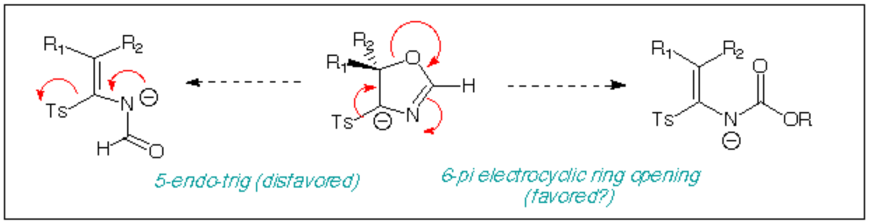
Tosylmethyl isocyanate (TosMIC) is a remarkable reagent developed by van Leusen and co-lworkers at the University of Groningen. One use of this reagent is for the one-carbon homologation of ketones to nitriles as illustrated below (*J. Org. Chem.* **1977**, *19*, 3114). In the illustrated application, Roush has applied this methodolgy to his synthesis of dendrobine (*J. Am. Chem. Soc.* **1980**, *4*, 1390).



Provide one or more plausible mechanisms for this transformation.



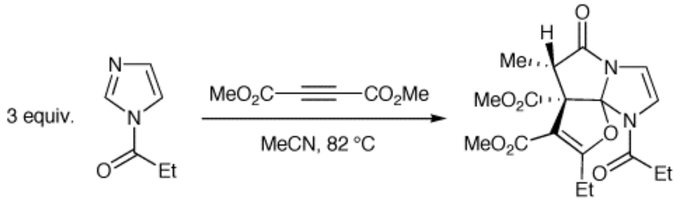
**Step A commentary:** This step should probably be viewed as an electrocyclic ring opening



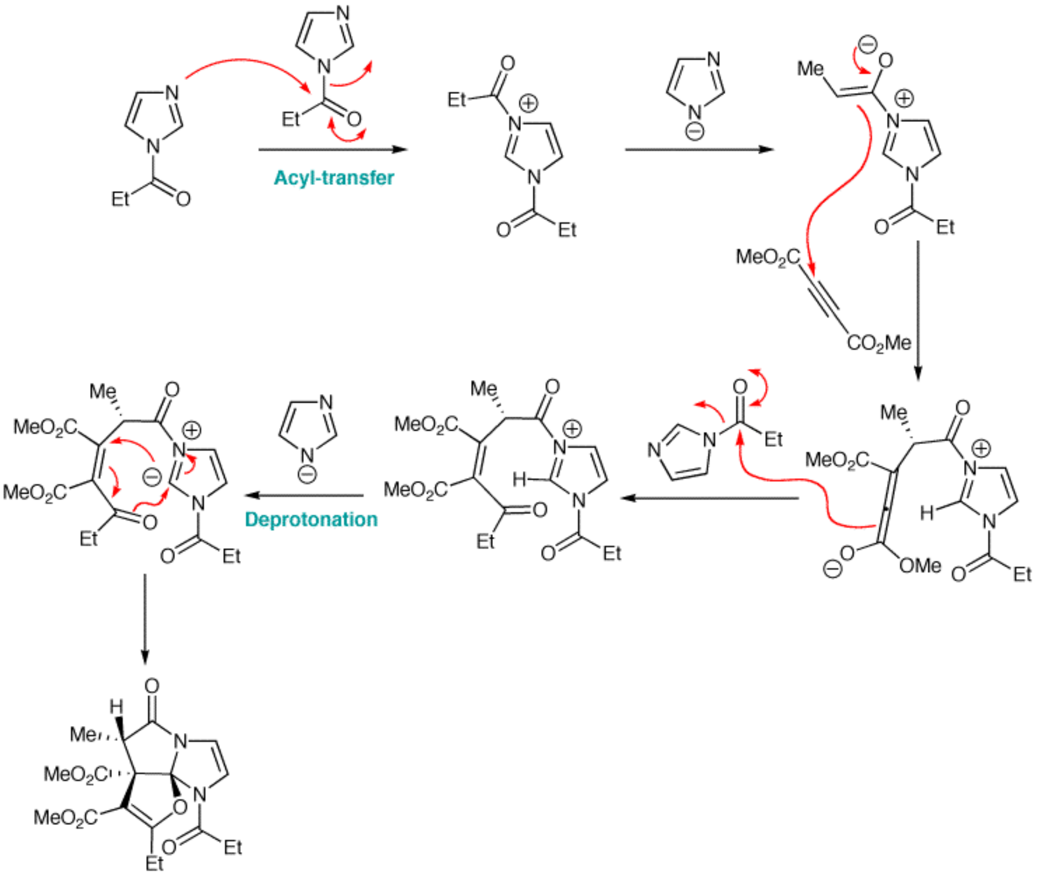
## Problem 413

Contributer: **Narendra Ambhaikar**
Citation: *SynLett* **1991**, 241

Knölker and co-workers (*Syn Lett.* **1991**, *4*, 241) have reported the diastereoselective annulation of 2-propanoylimidazole with dimethylacetylenedicarboxylate (DMAD) to yield the complex heterocycle shown below.

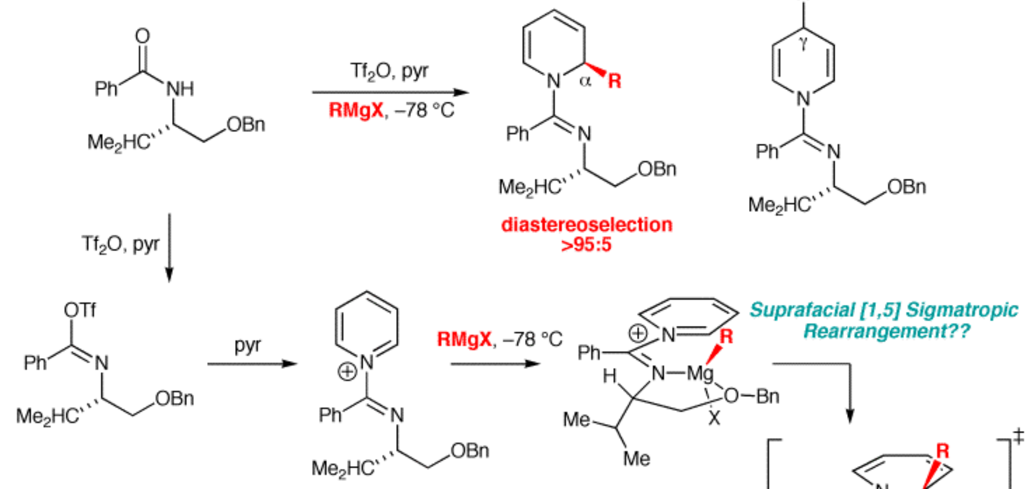


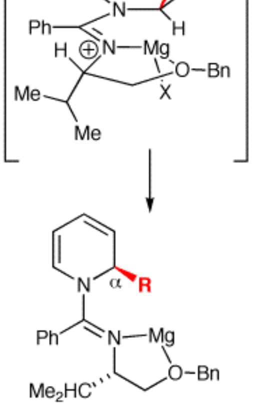
Provide a detailed mechanism for this reaction.



**Problem 434** Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2001**, *123*, 11829

Charette and co-workers recently reported a creative approach to the enantioselective synthesis α-substituted piperidine derivatives illustrated below (*JACS* **2001,** *123*, 11830). The alpha regioselectivities are generally >10:1 while the alpha diastereoselections are reported to be >95:5. Provide a detailed mechanism for the overall transformation. Provide a rationalization for the stereochemical outcome of the addition reaction. Three-dimensional drawings that illustrate chirality transfer should be provided.

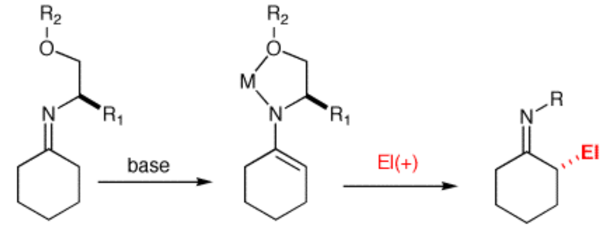




It appears that rather subtile conformational effects are operating to control selectivities between the alpha and alpha' positions. I presume that chelate organization is important to reaction diastereoselection. In this instance one might propose a suprafacial 1,5-sigmatropic rearrangement of the chelated organometal species. Steric effects might serve to orient the "R" substituent anti to the isopropyl moiety.

The use of these types of nitrogen-based chiral auxiliaries was introduced by both Meyers and Whitesell. Their applications in metalloenamine alkylation reactions is shown below.

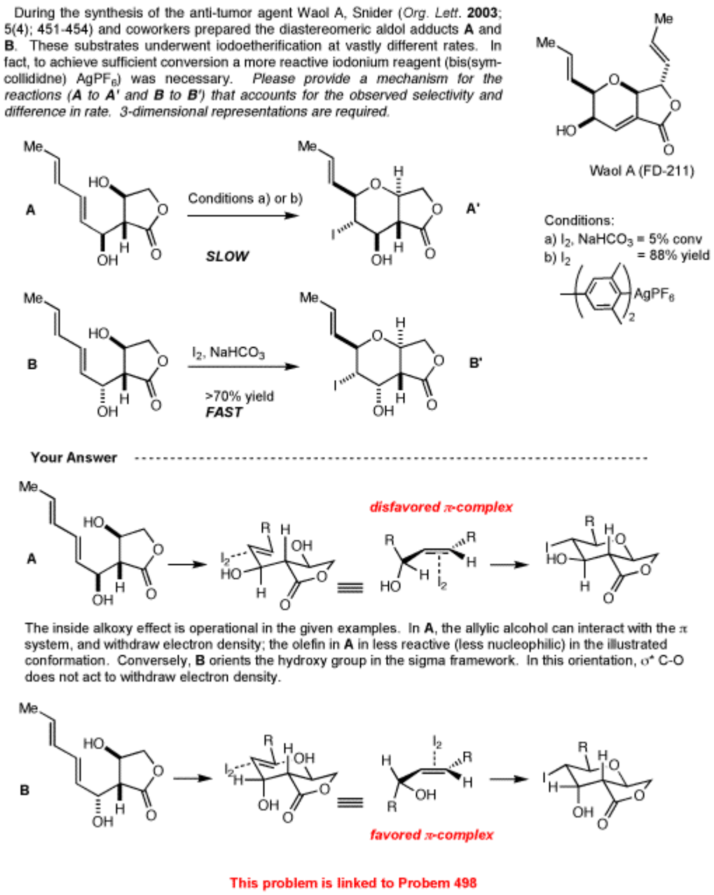
full papers:
- Meyers, *J. Org. Chem* ***1978***, *43*, 892
- Meyers, *J. Am. Chem. Soc* ***1981***, *103*, 3081
- Meyers, *J. Am. Chem. Soc* ***1981***, *103*, 3088



The base:
R–Li; RMgX; $R_2N$–Li

*Major Product*

**Problem 497** Contributer: **Jon Scheerer**
Citation: *Organic Lett.* **2003**, *5*, 451



During the synthesis of the anti-tumor agent Waol A, Snider (*Org. Lett.* **2003**; 5(4); 451-454) and coworkers prepared the diastereomeric aldol adducts **A** and **B**. These substrates underwent iodoetherification at vastly different rates. In fact, to achieve sufficient conversion a more reactive iodonium reagent (bis(sym-collididne) $AgPF_6$) was necessary. *Please provide a mechanism for the reactions (**A** to **A'** and **B** to **B'**) that accounts for the observed selectivity and difference in rate. 3-dimensional representations are required.*

Waol A (FD-211)

Conditions:
a) $I_2$, $NaHCO_3$ = 5% conv
b) $I_2$, bis(sym-collidine) $AgPF_6$ = 88% yield

**Your Answer**

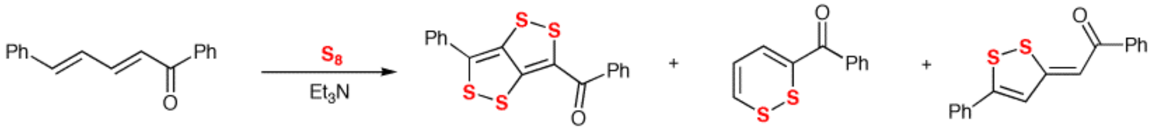
The inside alkoxy effect is operational in the given examples. In **A**, the allylic alcohol can interact with the π system, and withdraw electron density; the olefin in **A** in less reactive (less nucleophilic) in the illustrated conformation. Conversely, **B** orients the hydroxy group in the sigma framework. In this orientation, σ* C-O does not act to withdraw electron density.

This problem is linked to Probem 498

## Problem 581

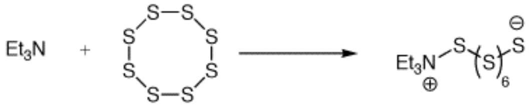
Contributer: **Ben Hafensteiner**
Citation: *Heterocycles* **1993**, *36*, 223-229

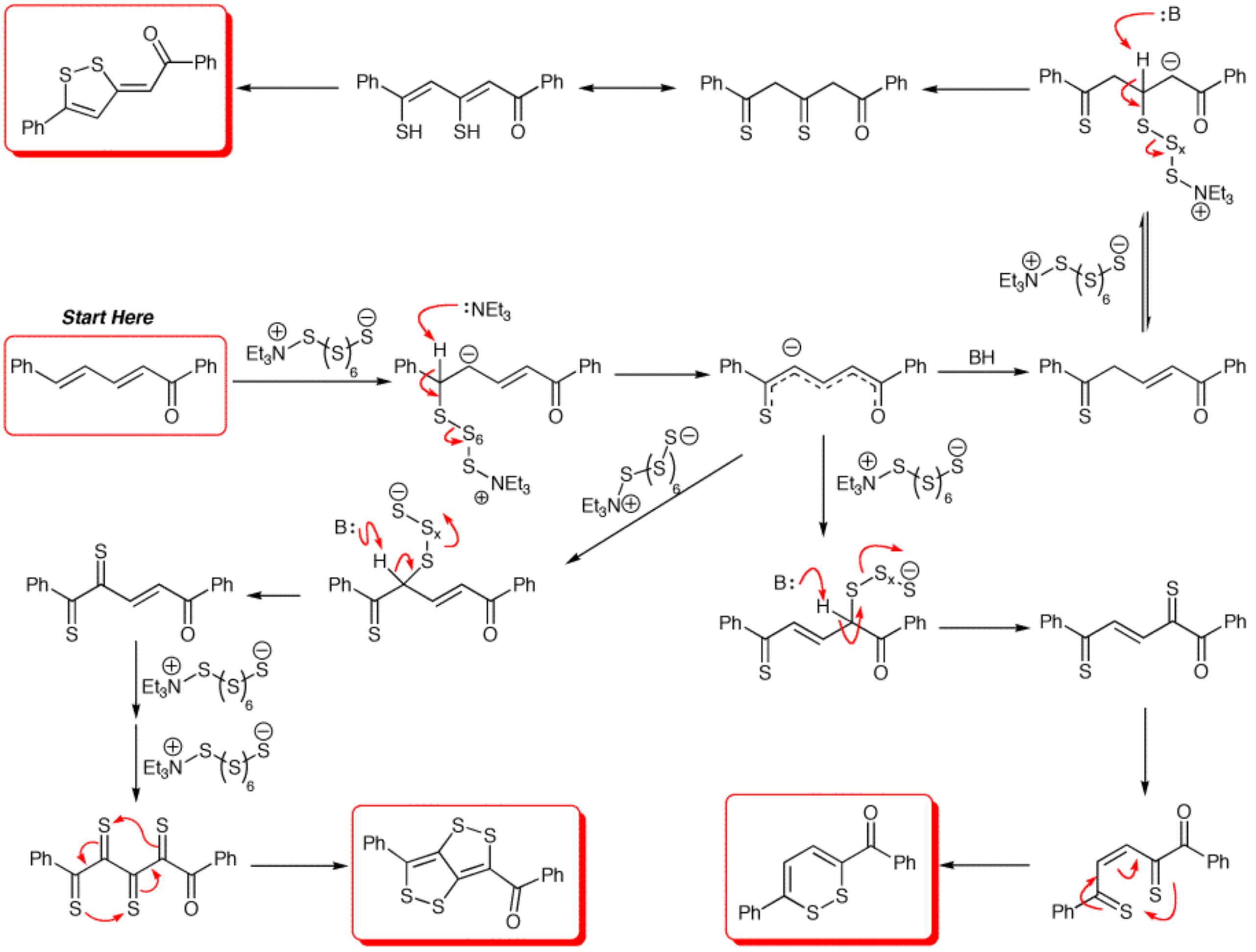
Sulfur oddities have intrigued chemists from the time the odiferous yellow compound was discovered. Here is problem derived from an investigation into elemental sulfur chemistry by the Purello group of the Universitá di Cantania (*Heterocycles*, **1993**, *36*, 223-229).



Provide one or more plausible mechanisms for this transformation identifiying all intermediates. Also, identify the active sulfur reagent in the above process.

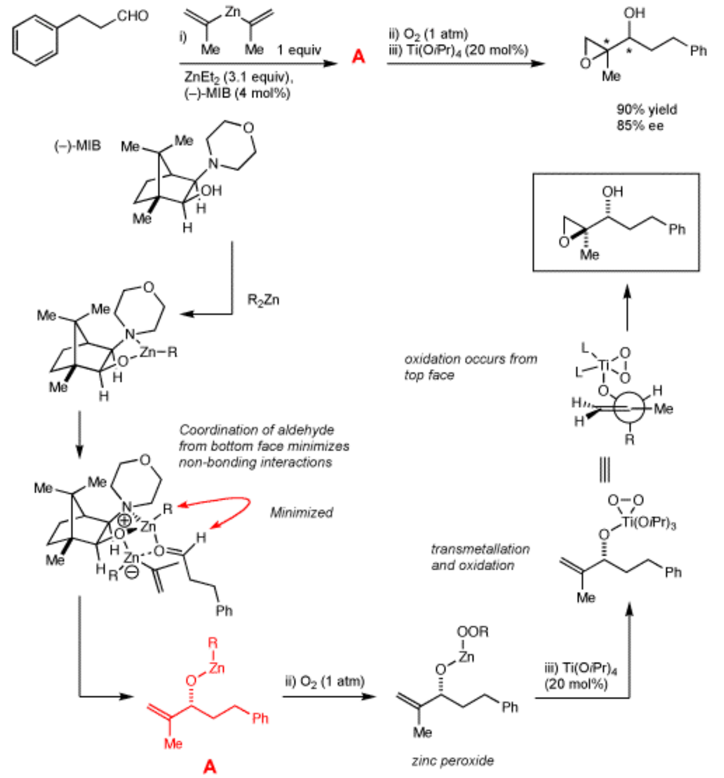
Activated Sufur:





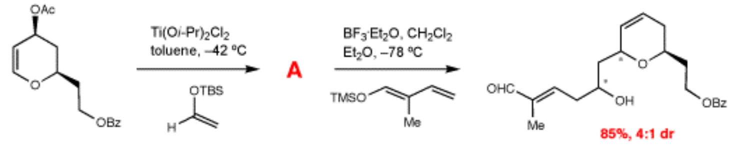
**Problem 628** Contributer: **Jon Scheerer**
Citation: *J. Am. Chem. Soc.* **2004**, *126*, 13608

A one-pot procedure for the enantioselective addition / diastereoselective epoxidation was recently developed in the laboratories of Patrick Walsh (*JACS*, **2004**, *126*, 13608.). This methodology can directly prepare up to 3contiguous stereocenters. Please provide a mechanism for this transformation and predict the stereochemistry of the product. Your anwser should use 3-D representations and highlight intermediate **A**. *(Hint: oxygen is known to insert into organozinc species, forming zinc peroxides and titanium can transmetallate with zinc. The organometallic aspects of this question may be de-emphasized in your answer.)*

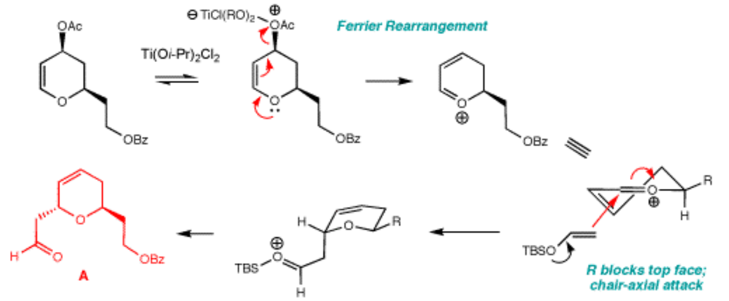

CHO
i)
Zn
Me
Me
1 equiv
ZnEt$_2$ (3.1 equiv),
(–)-MIB (4 mol%)
A
ii) O$_2$ (1 atm)
iii) Ti(O*i*Pr)$_4$ (20 mol%)
OH
O
Me
Ph
*
*
90% yield
85% ee
(–)-MIB
Me
Me
N
O
OH
H
H
R$_2$Zn
Zn–R
Coordination of aldehyde from bottom face minimizes non-bonding interactions
Minimized
Zn
R
H
Ph
oxidation occurs from top face
L
Ti
transmetallation and oxidation
Ti(O*i*Pr)$_3$
ii) O$_2$ (1 atm)
OOR
zinc peroxide
iii) Ti(O*i*Pr)$_4$ (20 mol%)
A

**Problem 630** Contributer: **Emily Balskus**
Citation: *Tetrahedron* **1995**, *51*, 9413

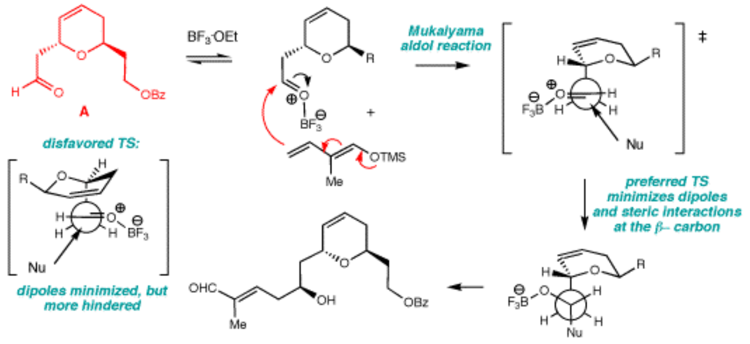
The Paterson group used the following reaction sequence in a synthesis of swinholide A (*Tetrahedron*, **1995**, *51*, 9413):



**Part A.** Provide the structure of intermediate **A** and the mechanism for its formation. Predict and account for the stereochemistry of **A** in your mechanism. Include 3-D drawings when relevant.

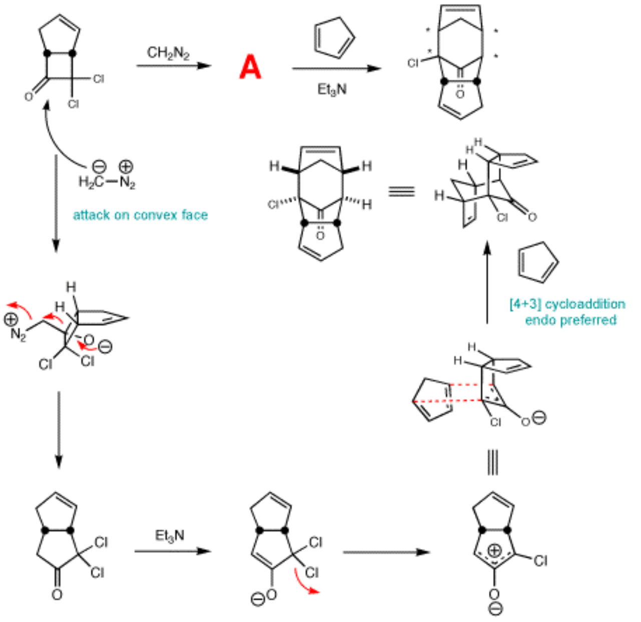


**Part B.** Provide a mechanism for the formation of the final product from intermediate **A**. Predict and account for the stereochemistry of the product in your mechanism. Include 3-D drawings when relevant.

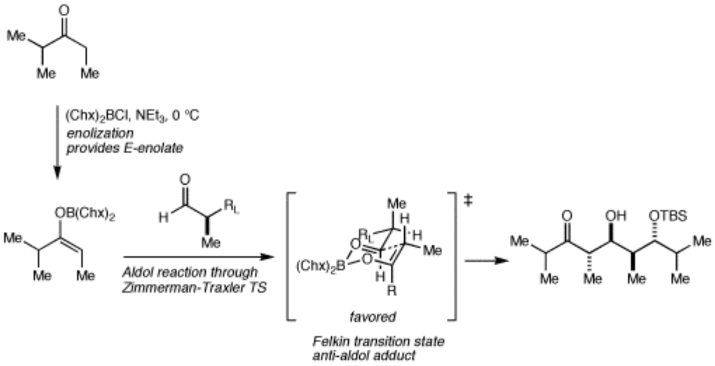

A
BF3·OEt
BF3
OTMS
Me
Mukaiyama aldol reaction
‡
F3B
Nu
disfavored TS:
dipoles minimized, but more hindered
preferred TS minimizes dipoles and steric interactions at the β– carbon
OHC
OH
OBz

**Problem 631** Contributer: **Jon Lawrence**
Citation: *Organic Lett.* **2001**, *36*, 2533

Harmata and co-workers reported the following interesting transformation (*Org. Lett.* **2001**, *3*, 2533.) Please provide a mechanism using 3-D representations where appropriate. Please identify intermediate **A** and assign the relative stereochemistry of the product.

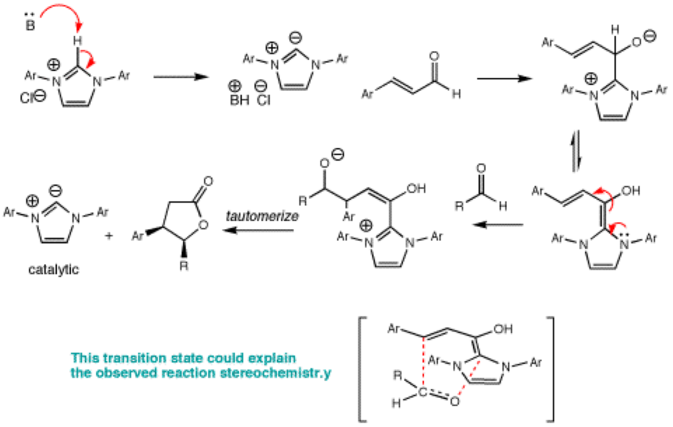


**Problem 696** Contributer: **David A. Evans**
Citation:



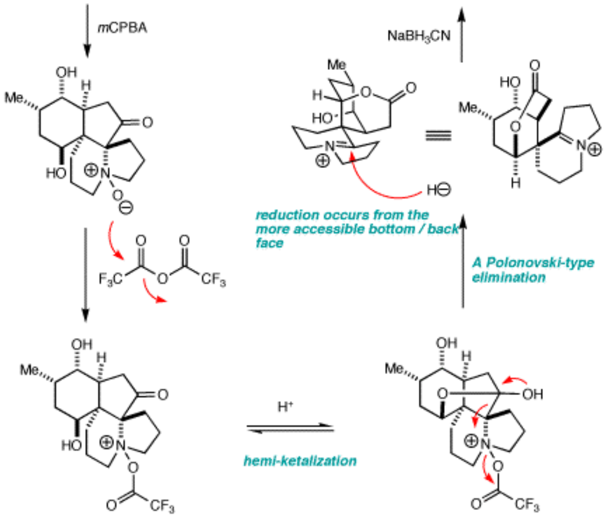
Felkin transition state
anti-aldol adduct

**Problem 697** Contributer: **David A. Evans**
Citation: *J. Am. Chem. Soc.* **2004**, *126*, 14379



This transition state could explain the observed reaction stereochemistr.y

**Problem 700** Contributer: **Jon Scheerer**
Citation: *J. Org. Chem.* **2002**, *67*, 5378



reduction occurs from the more accessible bottom / back face

A Polonovski-type elimination

hemi-ketalization

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